PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 249/08, 403/12, 417/12, A61K 31/495, C07D 249/12, C07C 249/14, C07D 257/06, 277/42

A1

(11) International Publication Number: **WO 98/31675**

(43) International Publication Date: 23 July 1998 (23.07.98)

(21) International Application Number: PCT/IB98/00046

(22) International Filing Date: 15 January 1998 (15.01.98)

(30) Priority Data:
08/786,376 17 January 1997 (17.01.97) US

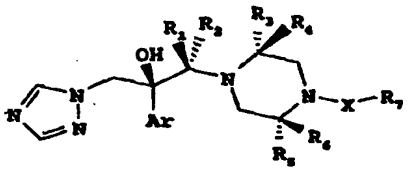
(71) Applicants: SYNPHAR LABORATORIES, INC. [CA/CA]; #2, 4290–91A Street, Edmonton, Alberta T6E 5V2 (CA). TAIHO PHARMACEUTICAL CO., LTD. [JP/JP]; 1–27, Kandanishiki–cho, Chiyoda–ku, Tokyo 101 (JP).

(72) Inventors: DANESHTALAB, Mohsen; 10419–10A Avenue, Edmonton, Alberta T6J 6G2 (CA). BATHINI, Yadagiri; 821–112B Street, Edmonton, Alberta T6J 6W3 (CA). NGUYEN, Dai; 4928–13 Avenue, Edmonton, Alberta T5L 6J9 (CA). SIDHU, Inderjit; 4807–18 Avenue, Edmonton, Alberta T6L 2Y4 (CA). ABEL, Mark; #301, 4024–114 Street, Edmonton, Alberta T6J 1M6 (CA). HA, Chan; 15726–108 Avenue, Edmonton, Alberta T5P 1A6 (CA). SALAMA, Sameeh; 9942–87 Avenue, Edmonton, Alberta T6E 2N7 (CA). KHAN, Jehangir; 217 RH, Michener Park, Edmonton, Alberta T6H 4M5 (CA). MICETICH, Ronald; 12 Braeside Terrace, Sherwood Park, Alberta T8A 3V6 (CA). FURUKAWA, Tetsuo; 43 Minamihara, Donari, Donari–cho, Itano–gun, Tokushima–ken 771–15 (JP). UNEMI, Norio; 34–14, Ohnishi Tainohama, Kitajima–cho, Itano–gun, Tokushima–ken 771–02 (JP).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NEW TRIAZOLES AS THERAPEUTIC AGENTS FOR FUNGAL INFECTIONS



(I)

(57) Abstract

A compound of formula (I), or an optical isomer or pharmaceutically acceptable salt thereof, is disclosed as well as a pharmaceutical composition and a method of treating or preventing a fungal infection using the compound.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

NEW TRIAZOLES AS THERAPEUTIC AGENTS FOR FUNGAL INFECTIONS

FIELD OF THE INVENTION

The present invention relates to the processes for the preparation of triazole compounds of formula I, i.e. 2-aryl-3-(4-substituted piperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ols, and their use in treating and or preventing the fungal infections in mammals preferably in humans.

BACKGROUND OF THE INVENTION

Recently the incidence of serious fungal infection has become very prominent in patients undergoing chemotherapy for cancer, organ transplants and patients with AIDS. Most of these infections are caused by opportunistic pathogens like *Candida spp.*, *Aspergillus spp.*, *Pneumocystis carnii* and *Cryptococcus neoformans.* The antifungal agents available in the market suffer with draw backs such as, toxicity, narrow spectrum of activity, fungistatic profile rather fungicidal. Some of them also exhibit drug-drug interactions and, as a result, therapy becomes very complex. In view of the high incidence of fungal infections in immunocompromised patients and the recent trend for the steady increase of the populations of these patients, demands for new antifungal agents with broad spectrum of activity and good pharmacokinetic properties have increased.

Within the available drugs to treat fungal infections, the azole class appears to be more promising. This class of compounds inhibit the biosynthesis of ergosterol in fungi, which is the main constituent of fungal cell membrane. Fluconazole and itraconazole are routinely used for maintenance of fungal infections. Although fluconazole is highly bioavailable, it is not active against filamentous fungi and emergence of fungal resistance has been reported recently (Antimicrob. Agents Chemother. 1995, **39**, 1-8). Itraconazol is active against filam ntous fungi, but it shows inconsistent results, maybe due to its high protein binding properti s and less

bioavailability. During the last few years, several research groups have been actively searching for new azoles with optimum pharmacokinetic properties. As a result, a number of candidate azoles have emerged, and some of them are undergoing preclinical and clinical evaluation. Some of the candidate azoles are disclosed in the following publications:

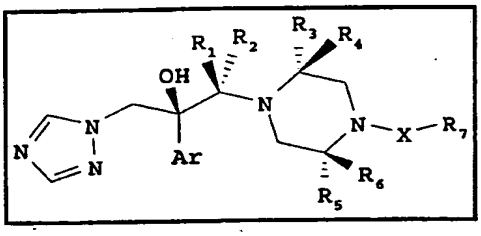
Sch 51048 (Drugs of the Future, 1995, **20**,241-247).
Sch 56592; Antimicrob. Agents Chemother. (1996, **40**, 1910-1913; 36th Interscience Conference Antimicrob. Agents Chemother. Sept. 1996, New Orleans, Abst. F87-F102).
UK-109,496 (Drugs of the Future, 1996, **21**, 266-271; EP 440372).
TAK-187; 36th Interscience Conference Antimicrob. Agents Chemother. Sept. 1996, New Orleans, Abst. F74; EP 567982).
KP-103 (36th Interscience Conference Antimicrob. Agents Chemother. Sept. 1996, New Orleans, Abst. F78, WO 94126734).
ER-30346 (Drugs of the Future, 1996, **21**, 20-24)

In the present invention, we report new triazoles with broad spectrum anti-fungal activity. The triazoles are particularly effective against systemic and lung invasive fungal infections.

SUMMARY OF THE INVENTION

The present invention relates to new triazole derivatives which can be utilised to treat or prevent fungal infections in animals, preferably in humans.

In accordance to the present invention, there is provided an antifungal triazole of the general formula **I**, i.e. 2-aryl-3-(4-substituted piperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)-2-ols and pharmaceutically acceptable salts thereof,



I

wherein:

Ar is a phenyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, CF_3 and OCF_3;

R_1 and R_2 are each independently hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, with the proviso that where R_1 is hydrogen, R_2 is other than hydrogen, and vice versa;

R_3 and R_4 are each independently hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, or R_3 and R_4 together form =S;

R_5 and R_6 are each independenly hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, or R_5 and R_6 together form =S;

X is selected from the group consisting of a direct bond, CO, CS, SO_2 and -N=N-;

R_7 is selected from the group consisting of

i) hydrogen,

ii) CN

iii) CHO

iv) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (1) C_1-

C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) C_1-C_4 alkoxy, (3) halogen, (4) formyl, (5) carboxyl, (6) C_1-C_4 acyloxy, (7) C_1-C_4 alkoxycarbonylamino, (8) phenyl- or naphthyl-oxycarbonylamino, (9) semicarbazido, (10) formamido, (11) thioformamido, (12) hydroxy, (13) nitro, (14) amino, (15) furyl, (16) triazolyl, (17) thienyl, (18) oxazolyl, (19) imidazolyl and (20) triazolone-yl,

v) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-4 heteroatoms each independently selected from the group consisting of N, O and S, which heterocycle is unsubstituted or ring-substituted with 1-3 substituents each independently selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) benzyl which is unsubstituted or substituted with 1-3 substituents selected from the group consisting of C_1-C_4 alkyl, CF_3, halogen and OCF_3, (3) halogen, (4) hydroxy, (5) nitro, (6) amino, (7) C_1-C_4 acylamino, (8) formyl, (9) formamido, (10) thioformamido, (11) C_1-C_4 alkoxycarbonylamino, (12) phenyl- or naphthyl-oxycarbonylamino and (13) semicarbazido,

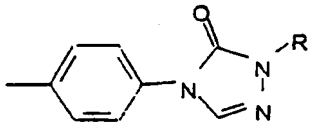
vi) NHR_8 wherein R_8 is selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f) C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl and (t) triazolone-yl, and (3) a 5- or 6-membered monocyclic or 8-

to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of hydroxy, halogen, amino and carboxyl,

vii) OR_9 wherein R_9 is selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f) C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl and (t) triazolone-yl and (3) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolon -yl, (c) naphthyl which is unsubstituted or substituted with 1-3

substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (d) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, (e) (C_1-C_4 alkyl)phenyl, (f) (C_1-C_4 alkyl)naphthyl, (g) hydroxy, (h) halogen, (i) amino and (j) carboxyl, and

viii) a group of the formula



wherein R is selected from the group consisting of (1) hydrogen, (2) C_1-C_{10} alkyl which is unsubstituted or substituted by 1-5 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (3) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f) C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl, (t) trizolone-yl, (u) CF_3 and (v) OCF_3, (4) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group

consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (c) naphthyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (d) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, (e) (C_1-C_4 alkyl)phenyl, (f) (C_1-C_4 alkyl)naphthyl, (g) hydroxy, (h) halogen, (i) amino and (j) carboxyl, (5) phenyl(C_1-C_4 alkyl) which is unsubstituted or ring-substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_5 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) halogen, (c) halo(C_1-C_4 alkyl), (d) C_1-C_4 alkoxy, (e) hydroxy, (f) amino, (g) carboxyl, (h) trifluormethoxyl, (i) trifluoromethyl, (j) tetrafluoroethyl, (k) tetrafluoroethoxyl,

(l) tetrafluoropropyl and (m) tetrafluoropropoxyl, (6) naphthyl(C_1-C_4 alkyl) which may be substituted with 1-6 substituents selected from (a) C_1-C_5 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) halogen, (c) (C_1-C_4 alkyl)halo, (d) C_1-C_4 alkoxy, (e) hydroxy, (f) amino, (g) carboxyl, (h) trifluormethoxyl, (i) trifluoromethyl, (j) tetrafluoroethyl, (k) tetrafluoroethoxyl, (l) tetrafluoropropyl and (m) tetrafluoropropoxyl, (7) methoxyl, (8) trifluormethoxyl, (9) trifluoromethyl, (10) trifluoroethyl, (11) tetrafluoroethyl, (12) tetrafluoroethoxyl, (13) tetrafluoropropyl and (14) tetrafluoropropoxyl.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the above definition of formula **I**, halogen is fluorine, chlorine, bromine or iodine. Preferred halogens are fluorine and chlorine.

C_1-C_4 alkyl is, for example, methyl, ethyl, propyl, 1-methylethyl, *n*-butyl, 1-methylethyl, isopropyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl, cyclopropyl and cyclobutyl. Preferred alkyls are methyl and ethyl.

Examples of **Ar** groups include, 4-fluorophenyl, 2-4-difluorophenyl, 2,4,6-trifluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2,4,6-trichlorophenyl, 4-trifluoromethylphenyl and 4-trifluoromethoxyphenyl. Preferred **Ar** groups are phenyl group having 1 or 2 substituents each independently selected from fluorine, chlorine, trifluoromethyl and trifluromethoxy. Most preferably, **Ar** is 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-trifluromethylphenyl or 4-trifluoromethoxyphenyl.

Examples of 5-or 6-membered monocyclic rings are 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 1-(1H)-1,2,4-triazolyl, 3-(1H)-1,2,4-triazolyl, 3-(4H)-1,2,4-triazolyl, 5-(1H)-1,2,4-triazolyl, 4-(4H)-1,2,4-triazolyl, 1,2,3-triazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-

thiadiazol-2-yl, 5-(1H)-tetrazolyl, 5-(2H)-tetrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl and 5-pyrimidyl.

Examples of 8- to 10-membered bicyclic heterocycle groups are 2-benzimidazolyl, 5-benzimidazolyl, 2-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, 2-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, imidazolo[4,5-b]pyridin-2-yl,imidazolo[4,5-b]pyridin-5-yl,oxazolo[5,4-b]pyridin-2-yl, oxazolo[5,4-b]pyridin-5-yl, oxazolo[5,4-b]pyridin-6-yl, thiazolo[5,4-b]pyridin-2-yl, thiazolo[5,4-b]pyridin-5-yl and thiazolo[5,4-b]pyridin-6-yl.

Triazolone-yl may be 2- or 5-substutitued 1,2,4-triazol-3-one, such as 2H-1,2,4-triazol-3-one-4-yl or 4H-1,2,4-triazol-3-one-2-yl.

Examples of R_1 include hydrogen, methyl, ethyl, propyl, hydroxymethyl, alkoxymethyl, fluoromethyl and trifluoromethyl. Preferably, R_1 is alkyl. Most preferably, R_1 is methyl.

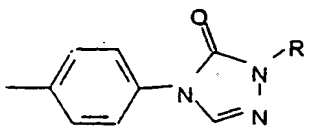
Examples of R_2 include hydrogen, methyl, ethyl, propyl, hydroxymethyl, alkoxymethyl, fluromethyl and trifluoromethyl. Preferably, R_2 is hydrogen.

Depending on the substituents in formula I, the compound may have one or more than one asymmetric centers, resulting in possible stereoisomers. This invention relates to single individual isomers as well as mixture of isomers.

When R_1 **and** R_2 are the same, formula I has one asymmetric center and there are two possible isomers, i.e. 2R and 2S isomers. This invention relates to mixtures as well as individual isomers. The most preferable isomer is the 2R isomer.

When R_1 **and** R_2 are different, formula I has two asymmetric centers, and there are four possible isomers, i.e. 2R,3R; 2R,3S; 2S,3R and 2S,3S. This invention relates to the mixture of isomers as well as individual isomers. The most preferred isomer in this situation is 2R,3R.

It is more preferred that R_7 is a group



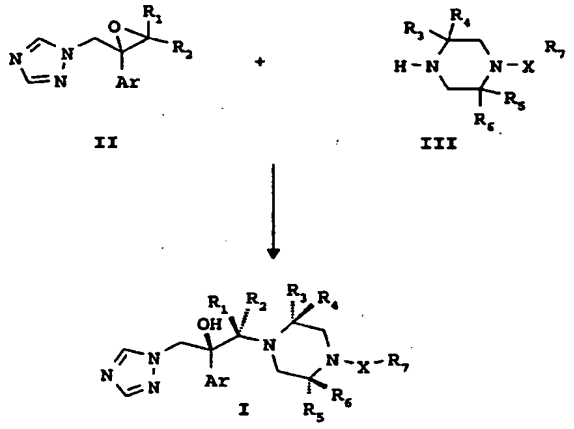
wherein **R** is as described above, and most preferred that the other groups additionally are as follows: **Ar** is 2,4-difluorophenyl, R_1 is methyl, and R_2 **through** R_6 are each hydrogen.

Specifically, the more preferred embodiments of the present invention include the compounds that are disclosed in Table 3. Those disclosed in Example Nos. 36-51 are more preferred, with Example Nos. 43, 47, 50 and 51 being the most preferred.

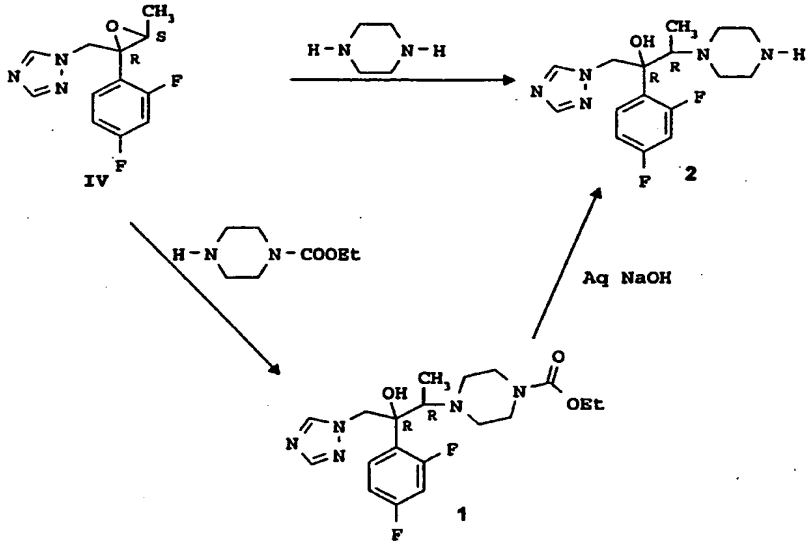
The compounds of formula **I** can be prepared by a convergent approach from the epoxide of formula **II** and the piperazino compound of formula **III** (see **Scheme 1**). The epoxides were prepared following the synthetic routes described in the literature (Chem. Pharm. Bull., 1993, **41**, 1035-1042).

The synthetic routes for the preparation of certain piperazino compounds of the formula **III** are disclosed in **Schemes 4-6** and **8**. The **Scheme 7** describes a linear synthetic route for preparing certain compounds of formula **I**. The epoxide of formula **II** and the piperazino compound of formula **III** were reacted in the presence of base such as sodium carbonate, potassium carbonate, cesium carbonate and the like. This reaction was also performed in the presence of lithium perchlorate and sodium perchlorate. The suitable solvents were chosen from acetonitrile, DMF, DMSO, THF, dichloromethane, chloroform, methanol, ethanol, isopropanol and *tert*-butanol. The most preferred solvents were DMF and acetonitrile. The temperature of the reaction varied from 60-180 °C, depending on the solvent and reactants. The most preferred temperature was 80-140 °C. The reactants were allowed to react to the completion or near to the completion of the reaction. The length of reaction time varied from few hours to several hours depending on the r actants, temperatur , and the solvent.

Scheme-1



Scheme-2



Certain compounds of formula I were prepared from a common intermediate, which forms Example 2 of this invention as described in **Scheme 3.** Example 2 was prepared from epoxide IV by two synthetic routes as depicted in **Scheme 2.** In the first route, a 1:1 molar ratio of epoxide and ethyl piperazine-1-carboxylate were reacted in the presence of potassium carbonate or lithium perchlorate in a suitable solvent. The obtained ester was hydrolysed with strong base such as sodium hydroxide or potassium hydroxide to give piperazinyl compound 2. In this reaction the resulting N-carboxylic acid undergoes in-situ decarboxylation to give the piperazino compound 2. In an alternate route, the piperazino compound was obtained in a single step from the reaction of epoxide IV with piperazine. In a typical procedure, the epoxide and excess piperazine were reacted in the presence of lithium perchlorate in a suitable solvent and at a desired temperature.

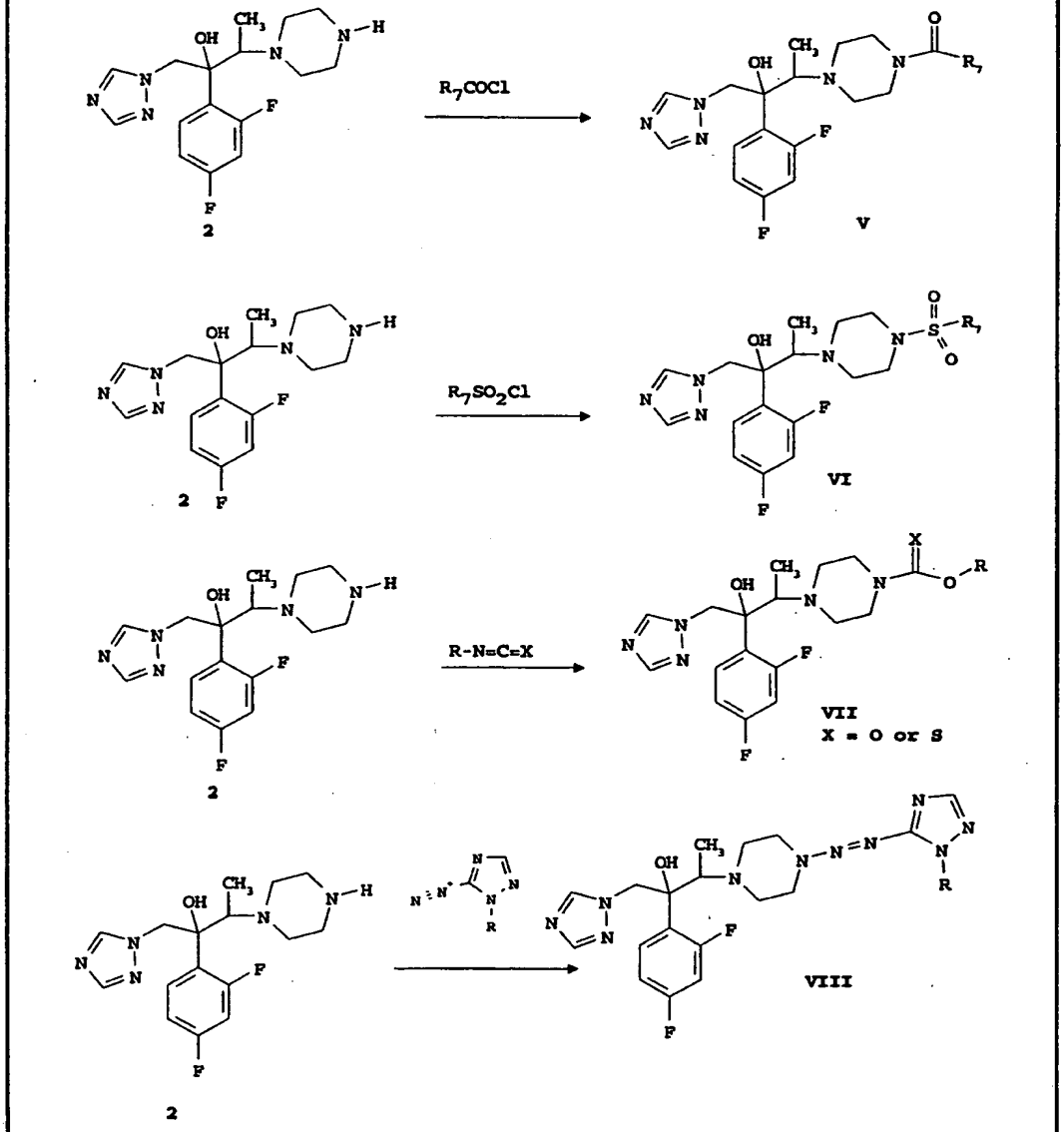
Certain compound of formula I wherein X is CO, SO_2, CS, or -N=N- were prepared as described in **Scheme 3.**

The compounds of formula I wherein X is CO were produced from the reaction of piperazinyl compound 2 with acid chloride (R_7COCl) in the presence of a base such as triethylamine, N-methylmorpholine, N,N-diisopropylethylamine. The reaction was carried out in an inert solvent at -20 °C to 80 °C. The most preferred solvents were dichloromethane, chloroform, tetrahydrofuran and acetonitrile. Most preferably the reaction was carried out at 0-25 °C. Certain compounds of formula I wherein X is SO_2 were prepared from the reaction of 2 and R_7-SO_2-Cl. In these reactions, R_7 is as described above.

Certain compounds of formula I wherein X is CO or CS and R_7 is OR were prepared from the reaction of piperazinyl compound 2 and isocyanates and isothiocyanates. In a typical reaction, a 1:1 molar ratio of compound and isocyanate or isothiocyanate were reacted in a suitable solvent at -15 to 45 °C. The preferred solvents were acetonitrile, ethyl acetate and dichloromethane. Th preferred temperatur was 0 to 25 °C. The reaction

time varied from few hours to sev ral hours depending on the reactants, solvent and temperature.

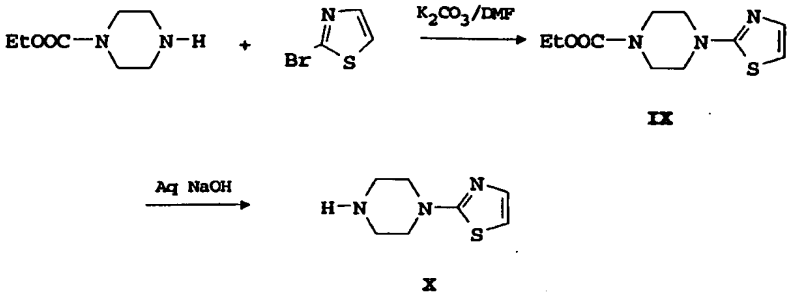
Scheme-3



The reaction of 1H or 2H-1,2,4-triazol-3-diazonium salt with the piperazinyl compound **2** gave the N-azo compound of formula **VIII.** This reaction was conducted at suitable temperature in suitable solvent in the presence of base like sodium hydroxide, potassium hydroxide and potassium carbonate.

Certain compounds of formula I wherein X is bond and R_7 is unsubstituted or substituted azole were prepared according to **Scheme 1** The synthetic routes followed for the preparation of piperazinyl azoles **X, XI, XII, XIII** and **XVI** are described in **Schemes 4-6**. In a typical procedure, piperazinyl azole and epoxide were heated in a suitable solvent in the presence of lithium perchlorate or potassium carbonate for 24-48 h. The molar ratio of the reactants varied from 1:1 to 1:5. After usual workup the product was purified by column chromatography.

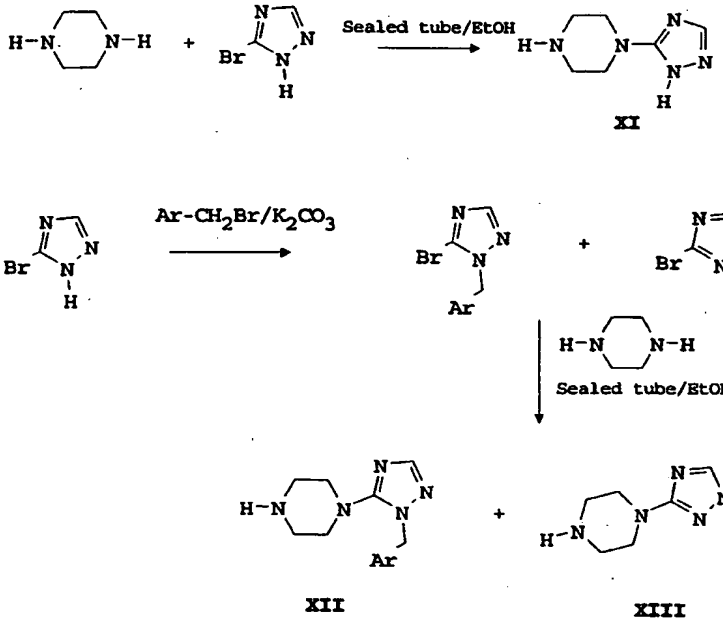
Scheme-4



IX

X

Scheme-5

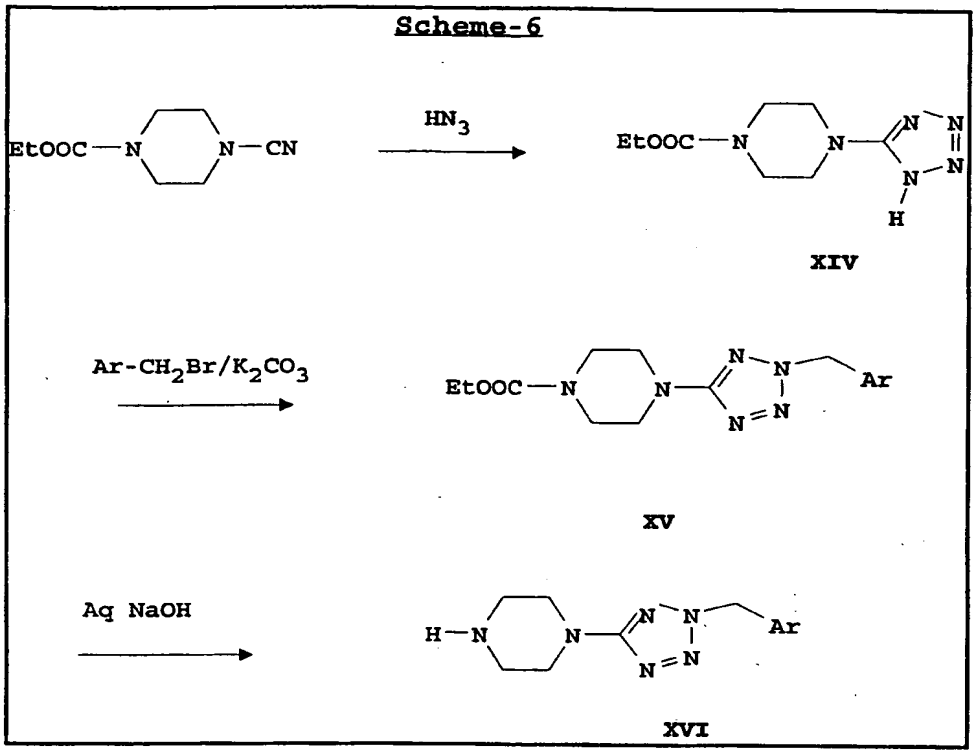


XI

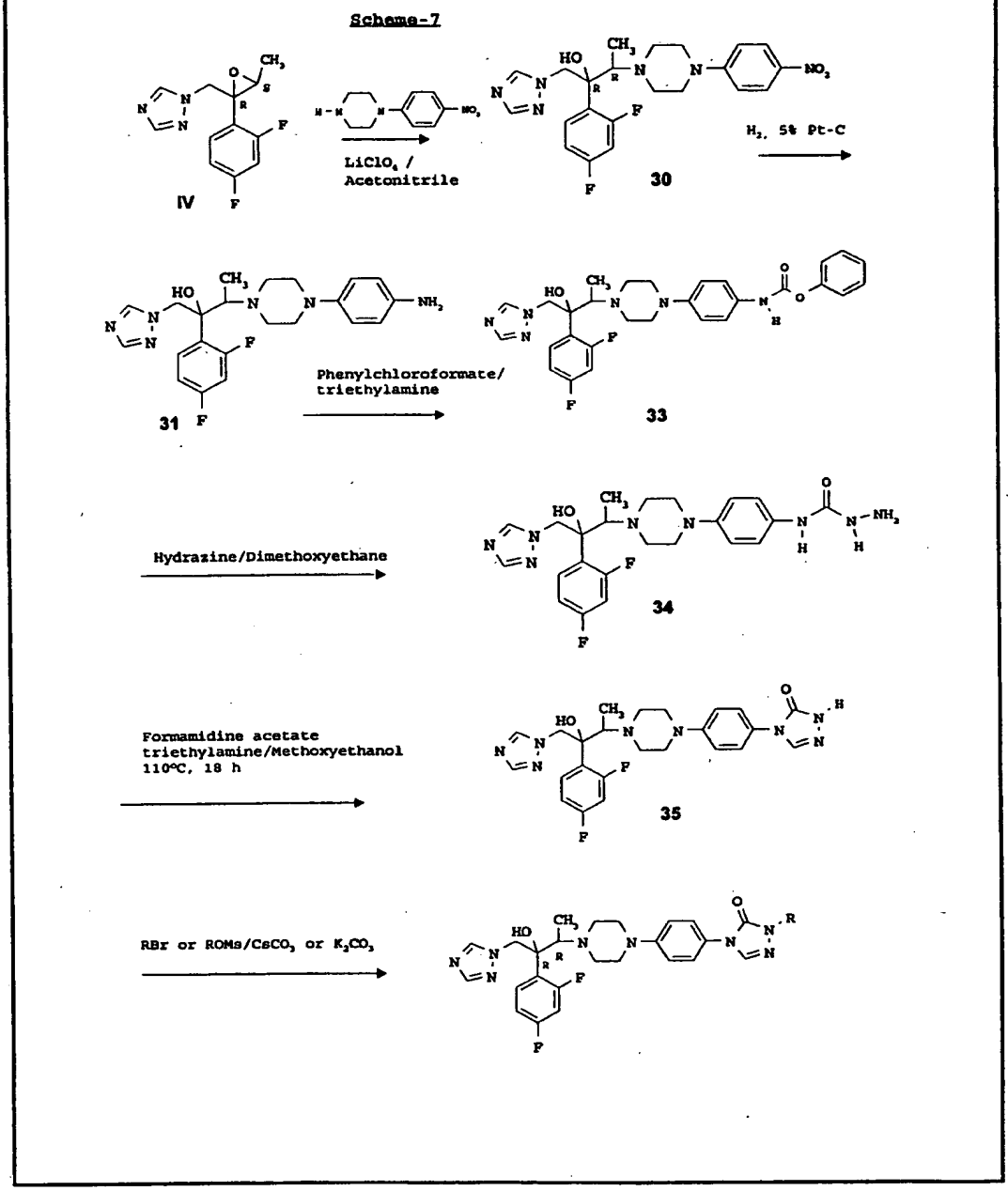
XII

XIII

Scheme-6

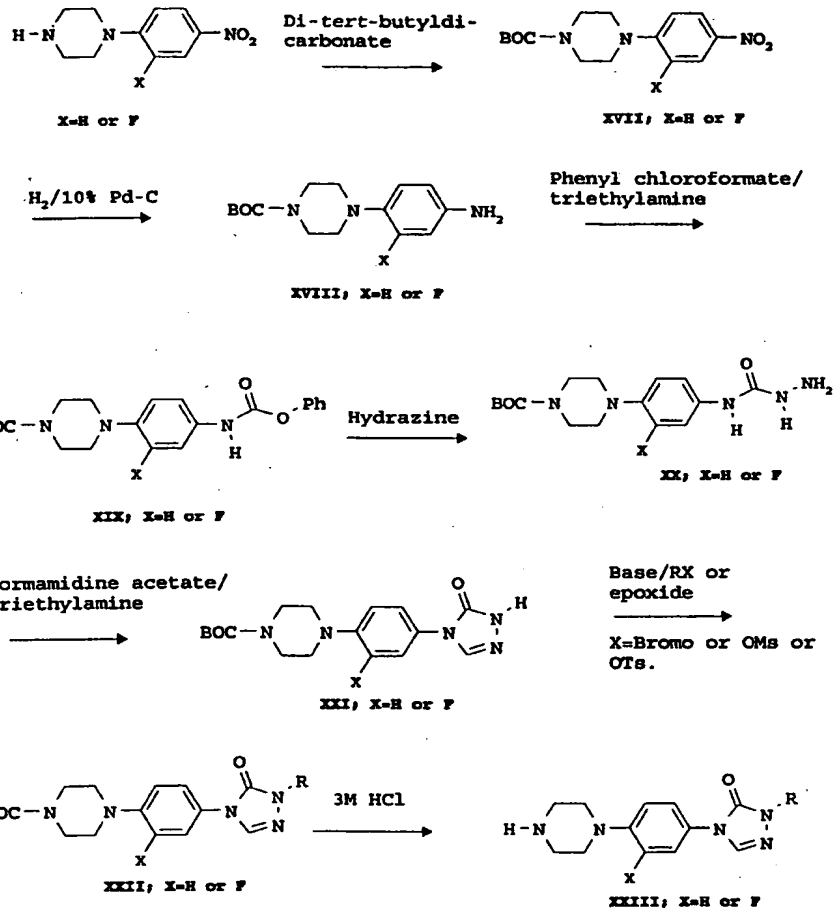


Certain compounds of formula I wherein X is a bond and R_7 is a 4-[2-substituted-1,2,4-triazol-3-one-4-yl]phenyl group were prepared in two independent synthetic routes. The first route involves the linear approach as described in **Scheme 7.** The intermediates formed during this synthesis are compounds of formula I, wherein X is bond and R_7 is phenyl group with substitution.


Scheme-7
IV
LiClO4 / Acetonitrile
30
H2, 5% Pt-C
31
Phenylchloroformate/ triethylamine
33
Hydrazine/Dimethoxyethane
34
Formamidine acetate triethylamine/Methoxyethanol 110°C, 18 h
35
RBr or ROMs/CsCO3 or K2CO3

The second synthetic route involves a more efficient convergent approach (**Scheme 1**). In a typical procedure, an appropriate epoxide of formula **II** and an appropriate piperazinyl derivative **XXIII** were reacted in the presence of lithium perchlorate in a suitable solvent and at a suitable temperature. The reactants were allowed to react to the completion of the reaction. The reaction time varied from few hours to several hours depending on the reactants. The epoxides used in this invention are known and were prepared by following the reported procedures. The piperazino compounds of formula **XXIII** were prepared as described in **Scheme 8**.

Scheme-8


Di-tert-butyldi-carbonate
X=H or F
XVII; X=H or F
H_2/10% Pd-C
Phenyl chloroformate/ triethylamine
XVIII; X=H or F
Hydrazine
XIX; X=H or F
XX; X=H or F
Formamidine acetate/ triethylamine
Base/RX or epoxide
X=Bromo or OMs or OTs.
XXI; X=H or F
3M HCl
XXII; X=H or F
XXIII; X=H or F

5

Pharmaceutically acceptable salts of formula I were prepared by mixing the solution of the free base with excess of acid at 0-25 °C. The precipitated salt was collected by filtration. In some cases the solvent was evaporated to dryness and the resulting crude salt was recrystallized in a suitable solvent. For the preparation of these acid addition salts, acids were selected from hydrochloric acid, hydrobromic acid, sulphuric acid, tartaric acid, succinic acid, fumaric acid, methanesulphonic acid or *p*-toluenesulphonic acid.

The compounds of the present invention were evaluated *in vitro* for their antifungal activity and were assessed based on minimum inhibitory concentration of the test compound, i.e. the concentration of the test compound at which growth of particular organism fails to occur. The MIC was determined after incubating the test compound with the strain for 48 h at 37 °C in an appropriate medium. The microorganisms used in this test include *Candida albicans*, *C. tropicalis*, *C. kefyr*, *C. krusei*, *C. guilliermondii*, *C. glabrata*, *Cryptococcus neoformans*, *Aspergillus niger* and *A. fumigatus*. *In vitro* data of certain representative compounds is provided in the following Table.

Table 1

***In vitro* activity of compounds of formula I**

Fungal strains	MIC of compounds of formula I, µg /ml								
	# 36	**# 40**	**# 41**	**# 42**	**# 43**	**# 44**	**# 46**	**Fluco-nazole**	**Itraco-nazole**
Candida albicans	0.09	0.09	0.09	0.09	0.048	0.048	0.048	0.78	0.09
C. tropicalis	0.09	0.048	0.09	0.09	0.048	0.048	0.048	0.39	0.09
C. kefyr	0.048	0.048	0.48	0.048	0.048	0.048	0.048	0.39	0.09

C. krusei	0.09	0.19	1.56	1.56	0.09	0.09	0.19	50	0.39
C. guillier-mondii	0.048	0.048	0.048	0.09	0.09	0.048	0.048	1.56	0.19
C. glabrata	0.09	0.39	0.78	12.5	0.78	1.56	0.39	12.5	0.19
Cryptococcus neoformans	0.048	0.48	0.48	0.19	0.048	0.048	0.048	1.56	0.39
Saccheromyces cerevisiae	0.19	0.09	0.19	0.39	0.09	0.048	0.09	6.25	0.39
A. niger	0.78	0.78	3.12	3.12	0.19	0.19	0.09	>100	0.39
Aspergillus fumigatus	0.39	0.39	0.78	0.39	0.19	0.048	0.048	>100	0.19

Certain selected compounds were evaluated *in-vivo* for their antifungal efficacy. Series of doses of test compounds were administered by oral, i.v and s.c. routes to infected mice, i.e mice that are inoculated with a strain of *Candida albicans* or *Aspergillus fumigatus*. Efficacy of test compound was determined based on survival of treated mice compared to control. The *in vivo* efficacy was assessed based on ED_{50} of the test compound. The following table provides ED_{50} of certain compounds for systemic infections of *C. albicans* and *A. fumigatus* in mice models.

Table 2

***In-vivo* activity of compounds of formula I**

	Therapeutic efficacy (ED_{50} mg/kg) in mice systemic infectinons	
Example #	*C. albicans*	*A. fumigatus*
36	8.01	>45
40	4.68	67.05
41	8.01	89.28
42	>90	71.14
43	1.57	42.3
46	56.02	>45

The compounds of formula I and their salts are anti-fungal agents, useful to treat or prevent topical, lung invasive, as well as systemic fungal infections in mammals including humans. For example they are useful in treating topical infections in man caused by species of *Candida, Trichophyton, Microsporum*, mucosal infections caused by species of *Candida,* and systemic infections caused by species of *Candida, Aspergillus, Cryptococcus, Pneumocystis, Histoplasma or Blastomyces.* The above compounds have shown impressive *in vivo* efficacy against mice systemic candidiosis, systemic aspergillosis and lung invasive aspergillosis.

When the compounds of the present invention or their pharmaceutically acceptable salts are used for treatment or prophylaxis of fungal infections in mammals including humans, they can be administered alone, but generally it is more preferred to administer the compounds in a pharmaceutical formulation. This formulation varies with intended route of administration. For example the compounds can be administered orally in the form of tablets, coated tablets, capsules, suspensions, solutions and the like. These oral preparations which contain the present compounds are prepared with excipients, binders, coloring agents, flavors, etc. which can be formulated in a manner known in the art.

The present compounds can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. These injections are sterile aqueous solutions which contain the antifungal agent with other substances, such as salts, glucose or an isotonic agent, and can be formulated in a conventional manner.

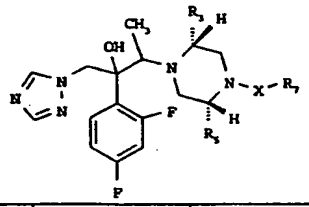
The amount of the present compounds incorporated into the pharmaceutical composition varies depending on the physical and chemical properties of the drug, dosage and route of administration. Preferably the oral formulations are prepared with 1 to 25% (w/w) antifungal agent and the injection formulation is prepared with 0.1 to 5% (w/w) of antifungal agent.

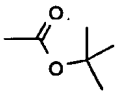
Alternativ ly, the antifungal ag nts also can be administered in the form of a suppository or pessary, or they may be applied topically in the form

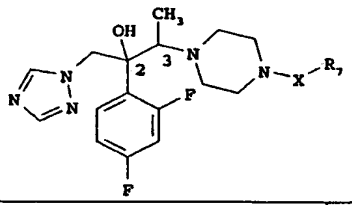
of lotion, solution, ointment, cream or dusting powder. Suppositories and ointments which contain 1-10% of active ingredient with a base, stabilizer or surfactant can be prepared in a conventional manner.

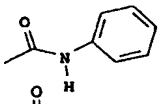
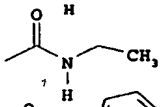
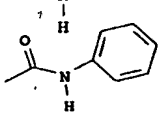
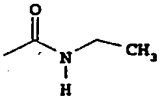
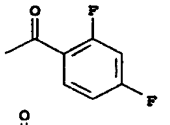
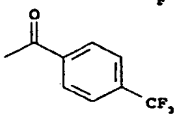
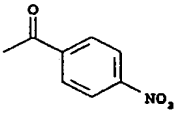
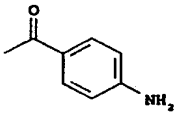
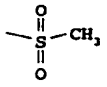
The dosage of the compound of formula I or its pharmaceutically acceptable salt can be suitably determined depending on the indivdual cases, taking symptoms, age, sex, disease status, patient condition, route of administration and the like into consideration. Usually the dosage can be 0.01-20 mg /kg in single or divided daily doses.

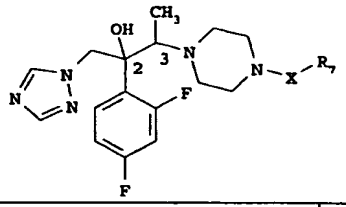
Table-3

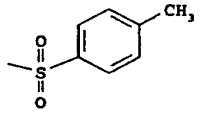
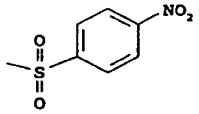
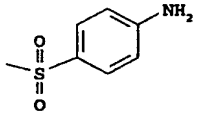
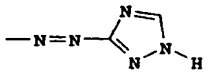
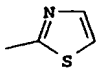
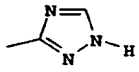
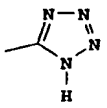


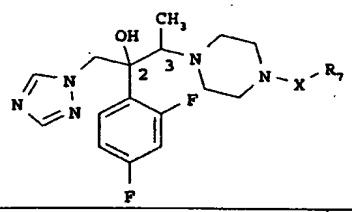
Example #	R_3	R_5	X-R_7	Configuration at C_2 and C_3
1	H	H	—COOEt	R,R
2	H	H	—H	R,R
3	H	H	—CN	R,R
4	H	H	—CHO	R,R
5	—CH_3	—CH_3	—H	R,R
6	—CH_3	—CH_3	—COOEt	R,R
7	H	H		R,R

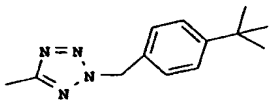
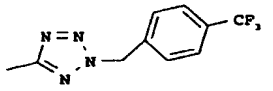
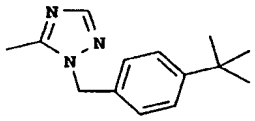
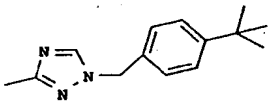
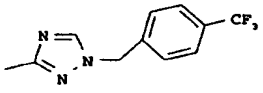
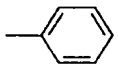
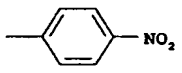
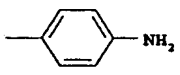


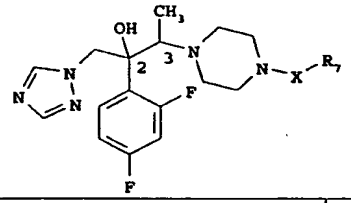
Example #	X-R_7	Configuration at C_2 and C_3
8		R,R
9		R,R
10		R,R
11		R,R
12		R,R
13		R,R
14		R,R
15		R,R
16		R,R

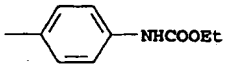
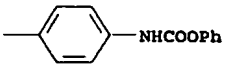
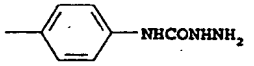
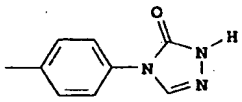
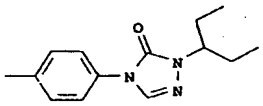
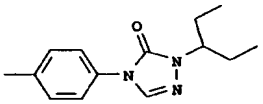
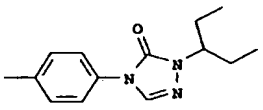
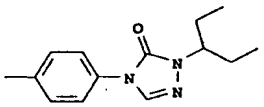


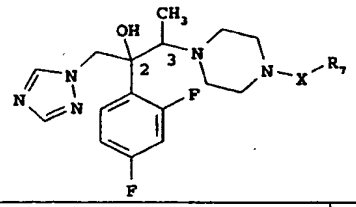
Example #	X-R_7	Configuration at C_2 and C_3
17		R,R
18		R,R
19		R,R
20		R,R
21		R,R
22		R,R
23		R,R

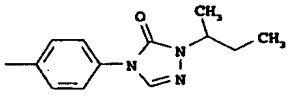
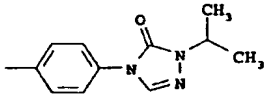
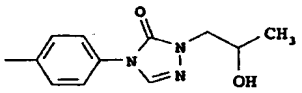
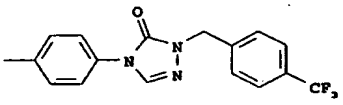
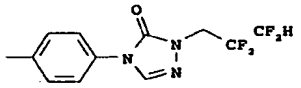
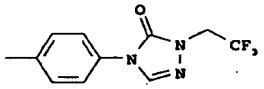
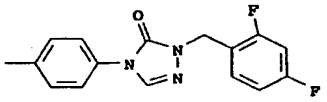
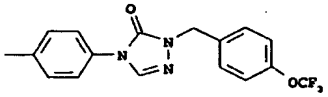


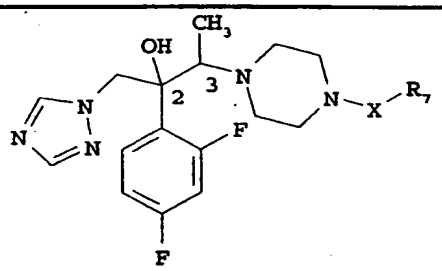
Example #	X=bond; R_7	Configuration at C_2 and C_3
24		R,R
25		R,R
26		R,R
27		R,R
28		R,R
29		R,R
30		R,R
31		R,R

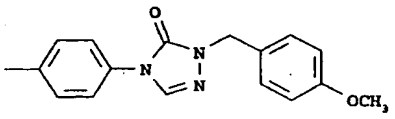
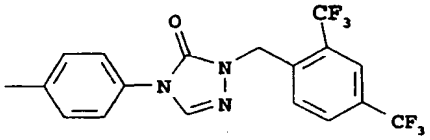
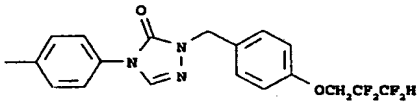
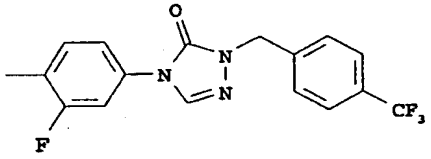


Example #	X=bond; R_7	Configuration at C_2 and C_3
32		R,R
33		R,R
34		R,R
35		R,R
36		R, R
37		S, R
38		S,S
39		R,S



Example #	X=bond; R_7	Configuration at C_2 and C_3
40		R,R
41		R,R
42		R,R
43		R,R
44		R,R
45		R,R
46		R,R
47		R,R



Example #	X=bond; R_7	Configuration at C_2 and C_3
48		R,R
49		R,R
50		R,R
51		R,R

EXAMPLES:

Example 1

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-ethoxycarbonylpiperazin-1-yl)-1-(1H-1,2,4-triaz l-1-yl)butan-2-ol:

A mixture of (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** (1.0 g, 4.0 mmol), ethyl piperazine-1-carboxylate (1.2 ml, 8 mmol) and potassium carbonate in DMF (5 ml) was heated at 120 °C for 18 h. After cooling the reaction mixture was poured onto crushed ice and extracted with ethyl acetate (3X30 ml). The combined extract was washed with water, brine, dried ($MgSO_4$) and concentrated and the resulting product was purified on a column of silica gel (hexane/EtOAc, 1:1) to give the title compound as off-white solid (400 mg, 24%).

m.p.: 182-183 °C.

^1H NMR ($CDCl_3$) δ: 0.90 (d, 3H, CH_3), 1.26 (t, 3H, CH_3), 2.31-2.49 (m, 2H, CH_2), 2.78-3.07 (m, 3H, CH_2 and CH), 3.40-3.59 (m, 4H, 2XCH_2), 4.15 (q, 2H, OCH_2), 4.9 (AB q, 2H, CH_2), 5.05 (s, 1H, OH), 6.66-6.84 (m, 2H, Ar-H), 7.36-7.51 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.92 (s,1H, Het-H).

FAB-MS: 410.2 (MH^+), calcd. $C_{19}H_{25}F_2N_5O_3$ 409.44.

Example 2

(2R,3R)-2-(2,4-Diflurophenyl)-3-(piperazin-1-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol:

A mixture of (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (1.0 g, 4.0 mmol), piperazine (860 mg, 10 mm0l) and lithium perchlorate (625 mg, 6 mmol) in acetonitrile (15 ml) was heated under reflux for 48 h. The solvent was removed under reduced pressure, the residue was treated with crushed ice and extracted with ethylacetate (3X30 ml). The combined organic extract was washed with water, brine, dried (Na_2SO_4) and concentrated to give the title compound as thick viscous gum (1.5 g, 78%). The title compound was also prepared by hydrolysis of 2R,3R-2-(2,4-difluorophenyl)-3-(4-ethoxycarbonylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1 -yl)butan-2-ol **1** with 2M sodium hydroxide solution.

^{1}H NMR ($CDCl_3$) δ: 0.97 (d, 3H, CH_3), 2.32-2.42 (m, 2H, CH_2), 2.66-2.90 (complex, 8H, 3XCH_2, CH and NH), 4.85 (AB q, 2H, CH_2), 6.68-6.83 (m, 2H, Ar-H), 7.42-7.55 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 8.0 (s, 1H, Het-H).
FAB-MS: 338.1 (MH^+), calcd. $C_{16}H_{21}F_2N_5O$ 337.38.

Example 3

(2R,3R)-3-(4-Cyanopiperazin-1-yl)-2-(2,4-diflurophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

To a cooled (0 °C) mixture of (2R,3R)-2-(2,4-difluorophenyl)-3-(piperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol **2** (250 mg, 0.74 mmol) and triethylamine (0.42 ml, 3 mmol) in acetonitrile (15 ml) was added cyanogen bromide (160 mg, 1.5 mmol) in acetonitrile (0.5 ml). The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. To the resulting residue water was added and extracted with ethyl acetate (3X20 ml). The combined organic extract was washed with water, brine and dried over magnesium sulphate. The solvent was removed and the product was purified on a column of silica gel (hexane/EtOAc, 1:1) to give the title compound as a colorless solid (150 mg, 56%).

m.p: 220 °C (decomp).
IR (Nujol) Vmax: 2210 cm^{-1}.
^{1}H NMR ($CDCl_3$) δ: 0.89 (d, 3H, CH_3), 2.52-2.61 (m, 2H, CH_2), 3.0-3.31 (m, 7H, 3XCH_2 and CH), 4.88-4.91 (m, 3H, CH_2 and OH), 6.66-6.78 (m, 2H, Ar-H), 7.3-7.5 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.87 (s, 1H, Het-H).
FAB-MS: 363.0 (MH^+), calcd. $C_{17}H_{20}F_2N_6O$ 362.39.

Example 4

(2R,3R)-2-(2,4-Diflurophenyl)-3-(4-formylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

A mixture of compound **2** (200 mg, 0.6 mmol) and potassium carbonate (248 mg, 1.8 mmol) in DMF (5 ml) was heated at 120 °C for 24 h. The contents

were poured into cold water and extracted with ethyl acetate (3X20 ml). The combined organic extract was washed with water, brine and dried over sodium suphate. The solvent was removed under reduced pressure and the resulting product was purified on a column of silica gel (EtOAc/MeOH; 98:2) to give the title compound as colorless solid (80 mg, 36%).

m.p: 118-120 °C.

^{1}H NMR ($CDCl_3$) δ: 0.90 (d, 3H, CH_3), 2.44-2.52 (m, 2H, CH_2), 2.93-3.11 (m, 3H, CH_2 and CH), 3.39-3.59 (m, 4H, 2XCH_2), 4.93-4.97 (m, 3H, CH_2 and OH), 6.66-6.81 (m, 2H, Ar-H), 7.36-7.48 (m, 1H, Ar-H), 7.79 (s, 1H, Het-H), 7.91 (s, 1H, Het-H), 8.02 (s, 1H, CHO).

FAB-MS: 366.1 (MH^+), calcd. $C_{17}H_{21}F_2N_5O_2$ 365.39.

Example 5

(2R,3R)-2-(2,4-Diflurophenyl)-3-(2,5-dimethylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The title compound **5** was obtained as a thick viscous oil in 58% yield from the reacton of (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and 2,5-dimethylpiperazine, by a similar method described in example **2**.

^{1}H NMR ($CDCl_3$) δ: 0.85-0.96 (3 d merged, 9H, 3XCH_3), 1.85-1.96 (m, 2H), 2.4-2.59 (m, 2H), 2.64-2.96 (m, 3H), 3.27-3.38 (m, 1H), 4.81 (AB q, 2H, CH_2), 5.50 (brs, 1H, OH), 6.69- 6.84 (m, 2H, Ar-H), 7.45-7.58 (m, 1H, Ar-H), 7.81 (s, 1H, Het-H), 8.02 (s, 1H, Het-H).

FAB-MS: 366.1 (MH^+), calcd. $C_{18}H_{25}F_2N_5O$ 365.43.

Example 6

(2R,3R)-2-(2,4-Diflurophenyl)-3-(2,5-dimethyl-4-thoxycarbonylpiperazin-1-yl)-1-(1H-1,2,4-triaz l-1-yl)butan-2-ol:

To a mixture of compound **5** (228 mg, 0.62 mmol) and triethylamine (0.18 ml, 1.24 mmol) in dichloromethane (10 ml) at 0 °C was added dropwise ethyl chloroformate (135 mg, 1.24 mmol) in dichloromethane (3 ml). The reaction mixture was stirred at 0 °C for 30 minutes and 1 h at room temperature. The contents were diluted with 30 ml of dichloromethane, washed with water, brine and dried over magnesium sulphate. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel. Elution with hexane/EtOAc (1:1) gave the title compound as an off-white solid (210 mg, 80%).

m.p: 57-59 °C.

^{1}H NMR ($CDCl_3$) δ: 0.94 (d, 3H, CH_3), 1.07-1.10 (m, 6H, 2XCH_3), 1.28 (t, 3H, CH_3), 2.34-2.46 (m, 1H), 2.76-2.82 (m, 1H), 2.96-3.09 (m, 2H), 3.21-3.31 (m, 1H), 3.67 (m, 1H), 3.98-4.27 (m, 3H), 4.80 (AB q, 2H), 5.13 (s, 1H, OH), 6.67-6.82 (m, 2H, Ar-H), 7.39-7.52 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.94 (s, 1H, Het-H).

FAB-MS: 438.3 (MH^+), calcd. $C_{21}H_{29}F_2N_5O_3$ 437.49.

Example 7

(2R,3R)-3-(4-*tert*-BOC-Piperazin-1-yl)-2-(2,4-diflurophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

To a mixture of compound **2** (150 mg, 0.44 mmol) and triethylamine (1.0 ml, 0.72 mmol) in dichloromehane (15 ml) was added di-*tert*-butyldicarbonate (110 mg, 0.48 mmol) at °C. The reaction mixture was stirred for 1h at 0 °C and 3 h at room temperature. Then diluted with chloroform (20 ml), washed with water, brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the resulting product was purified on a column of silica gel (EtOAc/hexane) to give the title compound as a colorless solid (160 mg, 82%).

m.p.: 138-139 °C.

^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 3H, CH_3), 1.46 (s, 9H, 3XCH_3), 2.34-2.40 (m, 2H, CH_2), 2.79-2.92 (m, 2H, CH_2), 2.97 (m, 1H, CH), 3.43 (m, 4H, 2XCH_2), 4.88 (AB q, 2H, CH_2), 5.11 (s, 1H, OH), 6.66-6.80 (m, 2H, Ar-H), 7.38-7.51 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.94 (s, 1H, Het-H).

FAB-MS 438.2 (MH^+); calcd. $C_{21}H_{29}F_2N_5O_3$ 437.49.

Example 8

(2R,3R)-3-(4-Anilinocarbonylpiperazin-1-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

To a ice cooled solution of (2R,3R)-2-(2,4-diflurophenyl)-3-(piperazin-1-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol **2** (150 mg, 0.44 mmol) in acetonitrile (10 ml) was added phenylisocyanate (60 mg, 0.5 mmol) in acetonitrile (4 ml). The reaction mixture was stirred at 0 °C for 2 h, diluted with 20 ml of ethyl acetate and successively washed with water, brine and dried over sodium sulphate. This organic extract was concentrated and the residue was purified by passing through a column of silica gel (hexane/EtOAc) to give the title compound as a colorless solid (170 mg, 84%).

m.p.: 98-100 °C (decomp).

^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 3H, CH_3), 2.5 (m, 2H, CH_2), 3.02 (m, 3H, CH_2 and CH), 3.52 (m, 4H, 2XCH_2), 4.8-5.1 (AB q and S merged, 3H, CH_2 and OH), 6.31 (br s, 1H, NH), 6.65-6.85 (m, 2H, Ar-H), 7.0-7.1 (m, 1H, Ar-H), 7.25-7.5 (m, 5H, Ar-H), 7.78 (s, 1H, Het-H), 7.92 (s, 1H, Het-H).

MS (FAB): 457.0 (MH^+), calcd. $C_{23}H_{26}F_2N_6O_2$ 456.49.

Example 9

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-ethylaminocarbonylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The tiltle compound was prepared similarly to example **8** starting from same piperazine derivative and ethylisocyanate. The product was obtained as a colorless solid in 75 % yield.

m.p.: 103-105 °C.

^{1}H NMR ($CDCl_3$) δ: 0.9 (d, 3H, CH_3), 1.14 (t, 3H, CH_3), 2.42 (m, 2H, CH_2), 2.8-3.1 (m and q merged, 3H, CH_2 and CH), 3.2-3.5 (m, 6H, 3XCH_2), (4.4 brs, 1H, NH), 4.88 (AB q, 2H, CH_2), 5.06 (s, 1H, OH), 6.7-6.9 (m, 2H, Ar-H), 7.45 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.93 (s, 1H, Het-H).

FAB-MS: 409.1 (MH^+), calcd. $C_{19}H_{26}F_2N_6O_2$ 408.45.

Example 10

(2R,3R)-3-(4-Anilinothiocarbonylpiperazin-1-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The title compound was prepared similarly to example **8** starting from same piperazine derivative **2** and phenylisothiocyanate. The product was obtained as a colorless solid in 80% yield.

m.p.: 106-108 °C.

^{1}H NMR ($CDCl_3$) δ: 0.88 (d, 3H, CH_3), 2.5 (m, 2H, CH_2), 2.9-3.1 (m, 3H, CH_2 and H), 3.84 (m, 4H, 2XCH_2), 4.8-5.1 (AB q and s merged, CH_2 and OH), 6.7-6.85 (m, 2H, Ar-H), 7.1-7.5 (m, 7H, 6 Ar-H and 1 NH), 7.77 (s, 1H, Het-H), 7.88 (s, 1H, Het-H).

FAB-MS: 473.3 (MH^+), calcd. $C_{23}H_{26}F_2N_6OS$ 472.56.

Example 11

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-ethylaminothiocarbonylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The title compound was prepared similarly to example **8** starting from same piperazine derivative **2** and ethylthioisocyanate. The product was obtained as a colorless solid in 85% yield.

m.p.: 96-98 °C.

1H NMR ($CDCl_3$) δ: 0.88 (d, 3H, CH_3), 1.25 (t, 3H, CH_3), 2.5 (m, 2H, CH_2), 3.06 (m, 3H, CH_2 and CH), 3.6-4.0 (q and m merged, 6H, 3XCH_2), 4.8-5.0 (AB q and s merged, 3H, CH_2 and OH), 5.39 (s, 1H, NH), 6.7-6.9 (m, 2H, Ar-H), 7.4- 7.5 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.89 (s, 1H, Het-H).

FAB-MS: 425.1 (MH^+), calcd. $C_{19}H_{26}F_2N_6OS$ 424.51.

Example 12

(2R,3R)-3-[4-(2,4-Difluorobenzoyl)piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

To a mixture of compound **2** (674 mg, 2 mmol) and triethylamine (0.55 ml, 4 mmol) in tetrahydrofuran (10 ml) was added dropwise 2,4-difluorobezoyl chloride (440 mg, 2.5 mmol) in 5 ml tetrahydrofuran at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and at room temperature for 18 h. The solvent was removed under reduced pressure, the residue was dissolved in dichloromethane (50 ml). The organic phase was washed with brine, dried over sodium sulphate. The solvent was removed under reduced pressure and the resulting product was purified on a column of silica gel (EtOAc/hexane, 9:1) to give the title compound as colorless prisms (448 mg, 47%).

m.p. = 63-65 °C.

1H NMR ($CDCl_3$) δ: 0.88 (d, J = 6.1 Hz, 3H), 2.04-2.59 (m, 2H); 2.99-3.09 (m, 4H); 3.35 (s, 2H); 3.72-4.10 (m, 1H) 4.91 (s, 2H); 5.01 (s, 1H); 6.65-7.00 (m, 5H); 7.34-7.48 (m, 1H); 7.77 (s, 1H); 7.9 (s, 1H).

FAB-MS: 478.3 (MH^+), calcd. $C_{23}H_{23}F_4N_5O_2$ 477.46.

Example 13

(2R,3R)-2-(2,4-Difluorophenyl)-1(1H-1,2,4-triazol-1-yl)-3-[4-(4-trifluoromethylbenzoyl)piperazin-1-yl]butan-2-ol.

The xample **13** was prepared form the reaction of piperazino derivative **2** and 4-(trifluoromethyl)benzoyl chloride by following the similar procedure described for the example **12.**

Colorless prisms, m.p.: 88-90 °C, Yield 87%.

^{1}H NMR ($CDCl_3$) δ: 0.88 (d, J = 6.5 Hz, 3H); 2.39-2.59 (m, 2H) 3.00-3.10 (m, 4H); 3.41-3.73 (m, 4H); 4.83 (AB q, 2H) 6.65-6.79 (m, 2H); 7.35-7.47 (m, 1H); 7.49 (d, J=8.0 Hz, 2H) 7.66 (d, J=8.0 Hz, 2H); 7.78 (s, 1H), 7.91 (s, 1H).

FAB-MS: 510.1 (MH^+), Calcd. $C_{24}H_{24}F_5N_5O_2$ 509.48.

Example 14

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-nitrobenzoyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

The example **14** was prepared form the reaction of piperazino derivative **2** and 4-nitrobenzoyl chloride by following the similar procedure described for the example **12.** After column purification the product was obtained as brown prisms in 92% yield.

m.p. 90-92 °C.

^{1}H NMR ($CDCl_3$) δ: 0.88 (d, J = 6.5 Hz, 3H), 2.42-2.61 (m, 2H) 3.05-3.08 (m, 4H); 3.39-3.73 (m, 3H); 4.92 (s, 3H) 6.66-6.78 (m, 2H); 7.34-7.47 (m, 1H); 7.55 (d, J = 8.6 Hz, 2H) 7.77 (s, 1H); 7.88 (s, 1H); 8.26 (d, J = 8.6 Hz, 2H).

FAB-MS: 487.0 (MH^+),$C_{23}H_{24}F_2N_6O_4$ 486.42.

Example 15

(2R,3R)-3-[4-(4-Aminobenzoyl)piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

A solution of nitrocompound **14** (487 mg, 1.0 mmol) in ethyl acetate (95 ml) was hydrogenated over 10% Pd-C (50 mg) at 45 psi pr ssure and room

temperature for 6 h. The catalyst was removed by filtration and the filtrate was concentrated to give the amino compound **15** as a colorless solid (330 mg, 72%).

m.p.: 100-102 °C.

^{1}H NMR ($CDCl_3$) δ : 0.89 (d, J = 5.8 Hz, 3H); 2.42-2.47 (m, 2H) 2.88-3.06 (m, 3H); 3.63 (br, 4H); 3.09 (br, 2H) 4.82 (t, J = 16.3 Hz, 2H); 5.02 (br, 1H); 6.61 (d, J = 8.5 Hz, 2H) 6.73-6.79 (m, 2H); 7.22 (d, J = 8.5 Hz, 2H); 7.30-7.48 (m, 1H) 7.77 (s, 1H); 7.92 (s, 1H).

FAB-MS: 457.1 (MH^+), calcd. $C_{23}H_{26}F_2N_6O_2$ 456.46.

Example 16

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(*p*-toluenesulphonyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

To a mixture of piperazinyl compound **2** (146 mg, 0.43 mmol) and triethylamine in dichloromethane (5 ml) was added *p*-toluenesulphonyl chloride (51 mg, 0.45 mmol) in dichloromethane (1 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 15 minutes and 2 h at room temperature. Then the reaction mixture was diluted with chloroform (15 ml), washed with water, brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the resulting product was purified on a column of silica gel ($CHCl_3$/MeOH; 98:2) to give the title compound as a colorless solid (75 mg, 16%).

m.p.: 81-83 °C.

^{1}H NMR ($CDCl_3$) δ : 0.88 (d, J = 6.9 Hz, 3H), 2.44 (s, 3H), 2.48-2.57 (m, 2H), 2.92-3.08 (m, 7H), 4.74 (s, 2H), 4.83 (s, 1H), 6.64-6.76 (m, 2H), 7.29-7.36 (m, 3H), 7.63 (s, 1H), 7.68 (s, 1H), 7.74 (s, 1H), 7.80 (s, 1H).

FAB-MS: 491.9 (MH^+), calcd. $C_{23}H_{27}F_2N_5O_3S$ 491.55.

Exampl 17

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(methanesulphonyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The epoxide IV (300 mg, 1.19 mmol) and $LiClO_4$ (235 mg, 1.43 mmol) were dissolved in 12 mL dry acetonitrile and 1-methanesulfonylpiperazine (190 mg, 1.79 mmol) was added. The mixture was heated to reflux for 4 days, cooled and the solvent evaporated. The residue was dissolved in dichloromethane and then washed with water and brine. The solution was dried over Na_2SO_4 and the solvent evaporated. The crude reaction products were eluted through a silica gel column using 3% MeOH/97% EtOAc as eluent to give the title compound (180 mg, 36%) as a colorless solid.

m.p.: 83-85 °C.

^1H NMR ($CDCl_3$) δ: 0.91 (d, J = 6.4 Hz, 3H), 2.56-2.61 (m, 2H), 2.80 (s, 3H), 3.02-3.18 (m, 3H), 3.22-3.30 (m, 4H), 4.89 (s, 2H), 4.93 (s, 1H), 6.66-6.79 (m, 2H), 7.35-7.48 (m, 1H), 7.79 (s, 1H), 7.88 (s, 1H).

FAB-MS: 415.9 (MH^+), $C_{17}H_{23}F_2N_5O_3S$ 415.45

Example 18

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-nitrophenylsulphonyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.:

The title compound was prepared from piperazinyl compound **2** and p-nitrobenzenesulphonyl chloride by following the similar procedure described for example **12.** The product was obtained as tan needles in 38% yield after purification on a column of silica gel ($CHCl_3$/MeOH; 96:4) followed by recrystalization in ether.

m.p.: 160-162 °C.

^{1}H NMR ($CDCl_3$) δ : 0.87 (d, J = 6.7 Hz, 3H), 2.51-2.66 (m, 2H), 2.96-3.20 (m, 7H), 4.74 (s, 2H), 4.81 (s, 1H), 6.62-6.76 (m, 2H), 7.29-7.41 (m, 1H), 7.72 (s, 1H), 7.77 (s, 1H), 7.94-7.98 (m, 2H), 8.39-8.43 (m, 2H).
FAB-MS: 523.2 (MH^+), calcd. $C_{22}H_{24}F_2N_6O_5S$ 522.52.

Example 19

(2R,3R)-3-[4-(4-aminophenylsulphonyl)piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

A solution of nitrocompound **18** (230 mg, 0.44 mmol) in ethanol (10 ml) was hydrogenated over 10% Pd-C (25 mg) at 45 psi pressure and room temperature for 18 h. The catalyst was removed by filtration and the filtrate was concentrated and the resulting product was purified on a column of silica gel ($CHCl_3$/MeOH; 57:43) to give the amino compound **19** as a colorless solid (165 mg, 76%).

m.p.: 95-97 °C.
^{1}H NMR ($CDCl_3$) δ : 0.88 (2, J = 6.1 Hz, 3H), 2.48-2.58 (m, 2H), 2.96-3.09 (m, 7H), 4.14 (br, 2H), 4.75 (s, 2H), 4.86 (s, 1H), 6.63-6.77 (m, 4H), 7.31-7.43 (m, 1H), 7.52-7.57 (m, 2H), 7.74 (s, 1H), 7.83 (s, 1H).
FAB-MS: 493.5 (MH^+), calcd. $C_{22}H_{26}F_2N_6O_3S$ 492.54.

Example 20

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(3-azo-1H-1,2,4-triazolyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

To a cooled solution of 3-amino-1H-1,2,4-triazole (378 mg, 4.5 mmol) in concentrated hydrochloric acid (1 ml) was added sodium nitrite (310 mg, 4.5 mmol) in portions. The resulting diazonium salt was transferred to a flask containing compound **2** (1 g, 3.0 mmol) in 20 ml of 3:1 mixture of 10% sodium hydroxide solution and tetrahydrofuran. Th resulting reaction mixture was stirred at room temperature for 2 h and extracted with chloroform (3X25

ml). The combined organic extract was washed with water, brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the resulting product was purified on a column of silica gel to give the title compound as thick viscous gum (100 mg, 8%).

^{1}H NMR ($CDCl_3$) δ : 0.92 (d, 3H, CH_3), 2.65 (m, 2H, CH_2), 3.1-3.3 (m, 3H, CH_2 and CH), 4.0 (m, 4H, $2XCH_2$), 4.95 (m, 3H, CH2 and OH), 6.72-6.81 (m, 2H, Ar-H), 7.4-7.49 (m, 1H, Ar-H), 7.79 (s, 1H, Het-H), 7.91 (s, 1H, Het-H), 7.97 (s, 1H, Het-H).

FAB-MS: 433.2 (MH^+), calcd. $C_{18}H_{22}F_2N_{10}O$ 432.43.

Example 21

Ethyl 4-(2-thiazolyl)piperazine-1-carboxylate:

A mixture of 2-bromothiazole (1.64 g, 10 mmol), ethyl 1-piperazinecarboxylate (1.896, 12 mmol) and sodium iodide (1.498, 10 mmol) in N,N-dimethylformamide (10 ml) was heated at 120 °C for 18 h. After cooling, the solvent was removed under reduced pressure and the residue was treated with crushed ice. The desired product was precipitated as colorless solid, was isolated by filtration (2.2 g, 91%).

^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3H, CH_3), 3.48 (m, 4H, $2XCH_2$), 3.62 (m, 4H, $2XCH_2$), 4.17 (q, 2H, OCH_2), 6.60 (d, 1H, Het-H, J=3.5 Hz), 7.20 (d, 1H, Het-H, J=3.5 Hz)

2-(Piperazin-1-ylthiazole:

To a methanolic solution of ethyl 4-(2-thiazolyl)piperazine-1-carboxylate (2 g, 8 mmol), 20 ml of 10% sodium hydroxide solution was added. The resulting mixture was heated under reflux for 5 h. After cooling, the reaction mixture was concentrated under reduced pressure, the residue was diluted with water and extracted with chloroform (3 X 30 ml). The combined extract was wash d

with water, brine, dried (Na_2SO_4) and concentrated to give the title compound as a thick viscous liquid (1.2 g, 86%).

1H NMR ($CDCl_3$) δ: 1.68 (br s, 1H, NH), 2.98 (m, 4H, $2XCH_2$), 3.46 (m, $2XCH_2$), 6.56 (d, 1H, Het-H, J=3.5 Hz), 7.2 (d, 1H, Het-H, J=3.5 Hz).

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(2-thiazolyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

To a mixture of (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** (502 mg, 2 mmol) and lithium perchlorate (320 mg, 3 mmol) in acetonitrile (10 ml), 2-(piperazin-1-yl)thiazole (**X**)(507 mg, 3 mmol) was added. The resulting mixture was heated under reflux for 48 h. The reaction mixture was cooled, concentrated under reduced pressure. The residue was disolved in chloroform, washed with water, brine, dried (Na_2SO_4) and concentrated. The resulting product was purified on a column of silica gel using ethyl acetate and hexane (4:1) as eluent to give the title compound as colorless solid (650 mg, 77%).

m.p.: 180-181 °C.

^1H NMR ($CDCl_3$) δ: 0.93 (d, 3H, CH_3), 2.57 (m, 2H, CH_2), 3.05 (m, 3H, CH_2 and CH) 3.51 (m, 4H, $2XCH_2$), 4.92 (AB q, 2H, CH_2), 5.05 (s, 1H, OH), 6.58 (d, 1H, Het-H, J=3.5 Hz), 6.7-6.8 (m, 2H, Ar-H), 7.2 (d, 1H, Het-H, J=3.5 Hz), 7.4-7.5 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.93 (s, 1-H, Het-H).

FAB-MS: 421.0 (MH^+), calcd. $C_{19}H_{22}F_2N_6OS$ 420.482.

Example 22

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(1H-1,2,4-triazol-3-yl)piperazin-1-yl]-1-(1H-1,2,4,triazol-1-yl)butan-2-ol:

The title compound was prepared in 48% yield from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane and 3-(piperazin-1-yl)-1H-1,2,4-triazole (**XI**) in the pres nce of lithium p rchlorat

following the similar procedure described for example **21.**

m.p.: 71-73 °C.

^{1}H NMR ($CDCl_3$) δ: 0.91 (d, 3H, CH_3), 2.48-2.60 (m, 2H, CH2), 2.90 -3.03 (m, 3H, CH_2 and CH), 3.32-3.51 (m, 4H, 2XCH_2), 4.81-5.04 (m, 2H, CH_2), 5.20 (br, 2H), 6.67-6.86 (m, 2H, Ar-H), 7.35-7.58 (m, 1H, Ar-H), 7.72 (s, 1H, Het-H), 7.78 (s, 1H, Het-H), 8.01 (s, 1H, Het-H)

FAB-MS: 405.0 (MH^+), calcd. $C_{18}H_{22}F_2N_8O$ 404.36.

Example 23

(2R,3R)-2-(2,4-difluorophenyl)-3-[4-(1H-5-tetrazolyl)piperazin-1-yl]-1-(1H-1,2,4,triazol-1-yl)butan-2-ol:

A mixture of compound **3** (140 mg, 0.39 mmol), sodium azide (31 mg, 0.47 mmol) and ammonium chloride (25 mg, 0.47 mmol) in DMF (5 ml) was heated at 90 °C for 48 h. Solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3X10 ml). Combined organic extract was washed with water, brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the resulting product was purified on a column of silica gel to give the title compound as a off-white solid (30 mg, 19%).

m.p.: 104-105 °C.

^{1}H NMR ($CDCl_3$) δ: 0.93 (d, 3H, CH_3), 2.63 (m, 2H, CH_2), 3.07 (m, 3H, CH_2 and CH), 3.56 (m, 4H, 2XCH_2), 4.93 (AB q and s merged, 3H, CH_2 and OH), 6.70-6.77 (m, 2H, Ar-H), 7.42-7.45 (m, 1H, Ar-H), 7.80 (s, 1H, Het-H), 7.96 (s, 1H, Het-H).

FAB-MS: 406.3 (MH^+), calcd. $C_{17}H_{21}F_2N_9O$ 405.42

Exampl 24

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[2-(4-*tert*-butylb nzyl)-2H-tetrazol-5-yl]piperazin-1-y}-1-(1H-1,2,4-triazol-1yl)butan-2-ol:

The title compound was prepared from the epoxide **IV** and tetrazolylpiperazine **XVI** (Ar=4-*tetrt*-butylphenyl) by following the similar procedure described for example **21.**
After usual workup and column purification the title compound was obtained as a colorless solid in 36% yield.

m.p.: 99-101 °C.
^{1}H NMR ($CDCl_3$) δ : 0.94 (d, 3H, CH_3), 1.30 (s, 9H, 3XCH_3), 2.47-2.59 (m, 2H, CH2), 2.91-3.01 (m, 3H, CH2 and CH), 3.50 (m, 4H, 2XCH_2), 4.88 (AB q, 2H, CH_2), 5.12 (br s, 1H, OH), 5.53 (s, 2H, CH2), 6.67-6.81 (m, 2H, Ar-H), 7.29-7.48 (m, 5H, Ar-H), 7.79 (s, 1H, Het-H), 7.95 (s, 1H, Het-H).
FAB-MS: 552.2 (MH^+); calcd. $C_{28}H_{35}F_2N_9O$ 551.61.

Example 25

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-{4-[2-(4-trifluoromethylbenzyl)-2H-tetrazol-5-yl]piperazin-1-yl}butan-2-ol:

The title compound was prepared from the epoxide **IV** and tetrazolylpiperazine **XVI** (Ar = 4-(trifluoromethyl)phenyl) by following the similar procedure described for example **21.** After usual workup and column purification the title compound was obtained as a colorless solid in 30% yield.
m.p.: 71-72 °C.
^{1}H NMR ($CDCl_3$) δ : 0.93 (d, 3H, CH_3), 2.51-2.56 (m, 2H, CH_2), 2.96-3.02 (m, 3H, CH_2 and CH), 3.49 (m, 4H, 2XCH_2), 4.90 (AB q, 2H, CH_2), 5.07 (s, 1H, OH), 5.62 (s, 2H, CH_2), 6.68-6.77 (m, 2H, Ar-H), 7.43-7.65 (m, 5H, Ar-H), 7.78 (s, 1H, Het-H), 7.93 (s, 1H, Het-H).
FAB-MS: 564.1 (MH^+), calcd. $C_{25}H_{26}F_5N_9O$ 563.54.

Example 26

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[2-(4-*tert*-butylbenzyl)-2H-1,2,4-triazol-3-yl]piperazin-1-y}-1-(1H-1,2,4-triazol-1yl)butan-2-ol:

The title compound was prepared from the epoxide **IV** and triazolylpiperazine **XII** (Ar = 4-*tert*-butylphenyl) by following the similar procedure described for example **21**. After usual workup and column purification the title compound was obtained as a colorless solid in 45% yield.

m.p.: 73-75 °C.

^{1}H NMR ($CDCl_3$) δ : 0.93 (d, 3H), 1.30 (s, 9H), 2.49-2.59 (m, 2H), 2.95-3.07 (m, 3H), 3.12-3.14 (m, 4H), 4.78-4.95 (m, 2H), 5.04 (s, 1H), 5.15 (s, 2H), 6.66-6.80 (m, 2H), 7.12 (d, 2H, J=8.3 Hz), 7.34 (d, 2H, J=8.3 Hz), 7.35-7.49 (m, 1H), 7.69 (s,1H), 7.76 (s, 1H), 7.92 (s, 1H).

FAB-MS: 551.4 (MH^+), calcd. $C_{29}H_{36}F_2N_8O$ 550.66

Example 27

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[1-(4-*tert*-butylbenzyl)-1H-1,2,4-triazol-3-yl]piperazin-1-y}-1-(1H-1,2,4-triazol-1yl)butan-2-ol:

The title compound was prepared from the epoxide **IV** and triazolylpiperazine **XIII** (Ar = 4-*tert*-butylphenyl) by following the similar procedure described for example **21**. After usual workup and column purification the title compound was obtained as a colorless solid in 46% yield.

m.p.: 84-86 °C.

^{1}H NMR ($CDCl_3$): δ: 0.94 (d, 3H, CH_3), 1.30 (s, 9H, $3XCH_3$), 2.45-2.55 (m, 2H), 2.83- 3.01 (m, 3H), 3.42-3.48 (m, 4H), 4.79-4.97 (m, 2H), 5.11 (s, 2H), 5.22 (s, 1H), 6.67-6.81 (m, 2H), 7.16 (d, 2H, J=8.2 Hz), 7.36 (d, 2H, J=8.2 Hz), 7.41-7.53 (m, 1H), 7.66 (s, 1H), 7.78 (s, 1H), 7.97 (s, 1H).

FAB-MS: 551.3 (MH^+), calcd. $C_{29}H_{36}F_2N_8O$ 550.66.

Exampl 28

(2R,3R)-2-(2,4-Difluorophenyl) -1-(1H-1,2,4-triazol-1yl)-3-{4-[1-(4-trifluoromethylbenzyl)-1H-1,2,4-triazol-3- yl]piperazin-1-y}butan-2-ol:

The title compound was prepared from the epoxide IV and triazolylpiperazine XIII (Ar = 4-(trifluoromethyl)phenyl) by following the similar procedure described for example **21.** After usual workup and column purification the title compound was obtained as a colorless solid in 18% yield.

m.p.: 69-72 °C

^{1}H NMR ($CDCl_3$) δ: 0.96 (d, 3H, CH_3), 2.49-2.54 (m, 2H, CH_2), 2.88-2.99 (m, 3H, CH_2 and CH), 3.43 (m, 4H, 2XCH_2), 4.93 (AB q, 2H, CH_2), 4.98 (2 s merged , 3H, CH_2 and OH), 6.69-6.80 (m, 2H, Ar-H), 7.32-7.64 (m, 5H, Ar-H), 7.78 (2 s merged, 2H, Het-H), 7.98 (s, 1H, Het-H).

FAB-MS: 562.9 (MH^+), calcd. $C_{20}H_{27}F_5N_8O$ 562.56.

Example 29

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-phenylpiperazin-1-yl)-1-(1H-1,2,4,triazol-1-yl)butan-2-ol:

The title compound was prepared by opening of the epoxide IV with 1-phenylpiperazine in the presence of lithium perchlorate by following similar procedure described to example **21.** After column purification the compound was obtained as a colorless solid.

m.p.: 103-105 °C.

1H NMR ($CDCl_3$) δ: 0.99 (d, 3H, CH_3), 2.6 (m, 2H, CH_2), 2.9-3.05 (m, 3H, CH_2 and CH), 4.89 (AB q, 2H, CH_2), 5.23 (s, 1H, OH), 6.7-7.0 (complex, 5H, Ar-H), 7.2-7.3 (m, 2H, Ar-H), 7.5 (m, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.79 (s, 1H, Het-H), 7.97 (s, 1H, Het-H).

FAB-MS: 414.1 (MH^+), calcd. $C_{22}H_{25}F_2N_5O$ 413.47.

Exampl 30

(2R,3R)-2-(2,4-Difluoroph nyl)-3-[4-(4-nitrophenyl)pip razin-1-yl]-1-(1H-1,2,4,triazol-1-yl)butan-2-ol:

The title compound was prepared similarly to example **21** using the oxirane **IV**(600 mg, 2.4 mmol), 4-nitrophenylpiperazine (660 mg, 3.2 mmol) and lithium perchlorate (383 mg, 3.6 mmol) as starting materials. After usual workup, the crude reaction product was purified on a column of silica gel (EtOAc/hexane) to give the desired compound as light yellow solid (920 mg, 84%).

m.p. 148-150 °C

^{1}H NMR ($CDCl_3$) δ : 0.94 (d, 3H, CH_3), 2.58-2.64 (m, 2H,), 3.06-3.13 (m, 3H), 3.4-3.5 (m, 4H), 4.93 (AB q, 2H, CH_2), 5.04 (s, 1H, OH), 6.7-6.85 (m and d merged, 4H, Ar-H), 7.38-7.51 (m, 1H, Ar-H), 7.79 (s, 1H, Het-H), 7.91 (s, 1H, Het-H), 8.13 (d, 2H, Ar-H).

FAB-MS: 459.2 (MH^+), calcd. $C_{22}H_{24}F_2N_6O_3$ 458.47

Example 31

(2R,3R)-3-[4-(4-Aminophenyl)piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4,triazol-1-yl)butan-2-ol:

To a solution of nitrocompound **30** (600 mg, 1.3 mmol) in 50 ml of ethyl acetate, 120 mg of 5% platinum on charcoal was added. The reaction mixture was hydrogenated in Parr hydrogenator at room temperature and 45 psi pressure for 18 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The pure amino compound **31** was obtained by dissolving the product in ethyl acetate and precipitating by addition of hexane (530 mg, 95%).

m.p.: 150-151 °C.

^{1}H NMR ($CDCl_3$) δ : 0.98 (d, 3H, CH_3), 2.53-2.59 (m, 2H, CH_2), 2.89-3.04 (complex, 7H, 3XCH_2 and CH), 4.87 (AB q, 2H, CH_2), 6.6-6.9 (2d and m merged, 6H, Ar-H), 7.43-7.55 (m, 1H, Ar-H), 7.79 (s, 1H, Het-H), 7.98 (s, 1H, Het-H).

FAB-MS: 429.2 (MH^+), calcd. $C_{22}H_{26}F_2N_6O$ 428.487.

Example 32

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-ethoxycarbonylaminophenyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

To a cooled (0 °C) mixture of amine **31** (300 mg, 0.7 mmol) and triethylamine (0.4 ml) in dichloromethane (30 ml) was added ethyl chloroformate (160 mg, 1.5 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at 0 °C for 2 h, then diluted with 30 ml of chloroform, washed with water, brine and dried over sodium sulphate. The solvent was removed under reduced pressure, the residue was purified on a column of silica gel (hexane/EtOAc, 1:1 and 1:2) to give the title compound as amorphous solid (330 mg, 94%).

m.p. 90-92 °C.

^{1}H NMR ($CDCl_3$)δ: 0.99 (d, 3H, CH_3), 1.29 (t, 3H, CH_3, J=7 Hz), 2.58 (m, 2H, CH_2), 2.95 (m, 3H, CH_2 and CH), 4.2 (q, 2H, CH_2, J=7 Hz), 4.88 (AB q, 2H, CH2), 5.21 (s, 1H, OH), 6.44 (s, 1H, NH), 6.7-6.85 (m, 2H, Ar-H), 6.87 (d, 2H, Ar-H, J=8.9 Hz), 7.26 (d, 2H, Ar-H, J=8.9 Hz), 7.41-7.54 (m, 1H, Ar-H), 7.78 (s, 1H, Het-H), 7.97 (s, 1H, Het-H).

FAB-MS: 501.0 (MH^+), calcd. $C_{25}H_{30}F_2N_6O_3$ 500.55.

Example 33

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-phenoxycarbonylaminophenyl)piperazin-1-yl]-1-(1H-1,2,4,triazol-1-yl)butan-2-ol:

The title compound was prepared similarly to the above procedure using the amine **31**(428 mg, 1 mmol) and phenyl chloroformate (235 mg, 1.5 mmol) in the presence of triethylamine (0.4 ml). After usual workup and purification on a silica gel column, the product was obtained as a colorless solid (475 mg, 89%).

m.p.: 95-97 °C.

^{1}H NMR ($CDCl_3$) δ : 0.98 (d, 3H, CH_3), 2.58 (m, 2H, CH_2), 2.98 (m, 3H, CH_2 and CH), 3.15 (m, 4H, 2XCH_2), 4.88 (AB q, 2H, CH_2), 5.19 (s, 1H, OH), 6.7-7.0 (d and m merged, 4H, Ar-H), 7.2-7.6 (complex, 8H, Ar-H), 7.78 (s, 1H, Het-H), 7.96 (s, 1H, Het-H).

FAB-MS: 549.3 (MH^+), calcd. $C_{29}H_{30}F_2N_6O_3$ 548.594.

Example 34

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[4-(semicarbazid-4-yl)phenyl]piperazin-1-yl}-1-(1H-1,2,4,triazol-1-yl)butan-2-ol:

To a solution of compound **33** (400 mg, 0.73 mmol) in dimethoxyethane (10 ml) was added hydrazine (1 ml) dropwise at room temperature and stirred for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was treated with crushed ice. The precipitated product was isolated by filtration and washed with water and hexane to give the title compound as a colorless solid (300 mg, 85%).

m.p.: 180-182 °C.

^{1}H NMR ($CDCl_3$) δ: 0.99 (d, 3H, CH_3), 2.54-2.60 (m, 2H, CH_2), 2.90-3.0 (m, 3H, CH_2 and CH), 3.10 (m, 4H, 2XCH_2), 3.8 (br s, 2H, NH2), 4.88 (AB q, 2H,

CH_2), 5.7 (br s, 1H, OH), 6.09 s, 1H, NH), 6.7-6.9 (d and m merged, 4H, Ar-H), 7.3-7.6 (d and m merged, 3H, Ar-H), 7.8 (s, 1H, Het-H), 7.93 (br s, 1H, NH), 8.0 (s, 1H, Het-H).

FAB-MS: 487.0 (MH^+), calcd. $C_{23}H_{28}F_2N_8O_2$ 486.527.

Example 35

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-{4-[4-(2H-1,2,4-triazol-3-one-4-yl)phenyl]piperazin-1-yl}butan-2-ol.

To a mixture of semicarbazide **34** (486 mg, 1 mmol) and formamidine acetate (416 mg, 4 mmol) in methoxyethanol (5 ml), triethylamine (0.8 ml) was added. The reaction mixture was heated at 110 °C for 18 h. Solvent was removed under reduced pressure and the residue was treated with crushed ice, extracted with ethyl acetate (3 X 30 ml). The combined extract was successively washed with water and brine and dried over sodium sulphate. The solvent was removed under reduced pressure, the crude product was purified on a column of silica gel (EtOAc/MeOH, 9:1) to give the triazolone **35** as a crystaline solid (320 mg, 65%).

m.p.: 223-225 °C.

^1H NMR ($CDCl_3$) δ: 0.98 (d, 3H, CH_3, J=6.4 Hz), 2.57-2.63 (m, 2H, CH_2), 2.95-3.1 (m, 3H, CH_2 and CH), 4.9 (AB q, 2H, CH2), 5.14 (s, 1H, OH), 6.7-6.82 (m, 2H, Ar-H), 6.98 (d, 2H, Ar-H, J=8.9 Hz), 7.37 (d, 2H, J=8.9, Ar-H), 7.4-7.5 (m, 1H, Ar-H), 7.62 (s, 1H, Het-H), 7.79 (s, 1H, Het-H), 7.95 (s, 1H, Het-H).

FAB-MS: 497.0 (MH^+), calcd. $C_{24}H_{26}F_2N_8O_2$ 496.522

Example 36

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl]}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

To a mixture of triazolone **35** (248 mg, 0.5 mmol) and cesium carbonate (326 mg, 1 mmol) in DMF, 3-bromopentane (226 mg, 1.5 mmol) was added. The

reaction mixture was heated at 80 °C for 18 h and concentrated in vacuo. The residue was treated with crushed ice, extracted with ethyl acetate (3 X 30 ml). The combined extract was washed with brine, dried (Na_2SO_4) and the solvent was removed under rduced pressure. The resulting crude product was purified on a column of silica gel (hexane/EtOAc) to give the title compound **36** as a crystaline solid (240 mg, 85%).

The title compound was also prepared in an alternate method in a convergent approach according to **Scheme-1**. Thus a mixture of (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV**, piperazino compound **XXIII** (R= 3-pentyl) and lithium perchlorate were heated in acetonitrile for 48 h. After usual workup and chromatographic purification, the title compound was obtained in 75% yield.

m.p.: 143-145 °C.

1H NMR ($CDCl_3$)δ: 0.88 (t, 6H, $2XCH_3$), 0.98 (d, 3H, CH_3), 1.65-1.8 (m, 4H, $2XCH_2$), 2.60 (m, 2H, CH_2), 3.1 (m, 3H, CH_2 and CH), 3.2 (m, 4H, $2XCH_2$), 4.12 (m, 1H, CH), 4.9 (AB q, 2H, CH2), 5.18 (s, 1H, OH), 6.7-6.8 (m, 2H, Ar-H), 6.97 (d, 2H, Ar-H, J=9 Hz), 7.4-7.6 (d and m merged, 3H, Ar-H), 7.64 (s, 1H, Het-H), 7.79 (s, 1H, Het-H), 7.96 (s, 1H, Het-H).

FAB-MS: 567.3 (MH^+), calcd. $C_{29}H_{36}F_2N_8O_2$ 566.657.

Example 37

(2S,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

The title compound was prepared from (2S,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane and piperazino compound **XXIII** (R = 3-pentyl) by following the similar procedure described for the example **36.**

Yield 70%, colorless solid.

m.p.: 83-85 °C.

^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 6H, $2XCH_3$), 1.25 (d, 3H, CH_3), 1.65-1.84 (m, 4H, $2XCH_2$), 2.46 (m, 2H, CH_2), 2.75 (m, 2H, CH_2), 2.93 (m, 4H, $2XCH_2$), 3.19 (q, 1H, CH), 4.05 (m, 1H, CH), 4.44 (d, 1H, J=14 Hz), 4.95 (d, 1H, J=14 Hz), 4.98 (s, 1H, OH), 6.64-6.77 (m, 2H, Ar-H), 6.74 (d, 2H, Ar-H), 7.29-7.43 (m, 3H Ar-H), 7.59 (s, 1H, Het-H), 7.77 (s, 1H, Het-H), 7.93 (s, 1H, Het-H).

FAB-MS: 567.2 (MH^+), calcd. $C_{29}H_{36}F_2N_8O_2$ 566.657.

Example 38

(2S,3S)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

The title compound was prepared from (2S,3R)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane and piperazino compound **XXIII** (R=3-pentyl) by following the similar procedure described for the example **36.**

Yield 87%, off-white solid.

m.p.: 218-220 °C.

1H NMR($CDCl_3$) δ : 0.88 (t, 6H, $2XCH_3$), 0.97 (d, 3H, CH_3), 1.70-1.84 (m, 4H, $2XCH_2$), 2.63 (m, 2H, CH_2), 3.01 (m, 3H, CH_2 and CH), 3.22 (m, 4H, $2XCH_2$), 4.12 (m, 1H, CH), 4.90 (AB q, 2H, CH_2), 5.14 (s, 1H, OH), 6.69-6.82 (m, 2H, Ar-H), 6.96 (d, 2H, Ar-H), 7.40-7.49 (m and d merged, 3H, Ar-H), 7.63 (s, 1H, Het-H), 7.79 (s, 1H, Het-H), 7.95 (s, 1H, Het-H).

FAB-MS: 567.4 (MH^+), calcd. $C_{29}H_{36}F_2N_8O_2$ 566.657.

Example 39

(2R,3 S)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

The title compound was prepared from (2R,3R)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane and piperazino compound **XXIII** (R= 3-pentyl) by following the similar procedure described for the xampl **36.**

Yield 60%, colorless solid.

m.p.: 110-113 °C.

^{1}HNMR ($CDCl_3$) δ : 0.87 (t, 6H, $2XCH_3$), 1.25 (d, 3H, J=7 Hz), 1.69-1.87 (m, 4H, $2XCH_2$), 2.46 (m, 2H, CH_2), 2.75-2.95 (m, 6H, $3XCH_2$), 3.19 (q, 1H, J=7 Hz), 4.07 (m, 1H, CH), 4.45 (d, 1H, J=15 Hz), 4.94 (d, 1H, J=15 Hz), 5.03 (s, 1H, OH), 6.66-6.76 (m, 2H, Ar-H), 6.87 (d, 2H, Ar-H), 7.34-7.39 (d and m merged, 3H, Ar-H), 7.60 (s, 1H, Het-H), 7.77 (s, 1H, Het-H), 7.93 (s, 1H, Het-H).

FAB-MS: 567.1 (MH^+), calcd. $C_{29}H_{36}F_2N_8O_2$ 566.657.

Example 40

(2R,3R)-3-[4-{4-[2-(2-Butyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

The example **40** was prepared similarly to the above procedure by alkylation of triazolone **35** with 2-bromobutane in the presence of cesium carbonate. After column chromatography the product was obtained as a colorless solid. Yield 88%.

m.p.: 156-157 °C.

^{1}H NMR ($CDCl_3$) δ : 0.90 (t, 3H, CH_3), 0.98 (d, 3H, CH_3), 1.6-1.9 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 3.0 (m, 3H, CH_2 and CH), 3.22 (m, 4H, $2XCH_2$), 4.29 (m, 1H, CH), 4.9 (AB q, 2H, CH_2), 5.14 (s, 1H, OH), 6.65-6.85 (m, 2H, Ar-H), 6.96 (d, 2H, Ar-H, J=8.9 Hz), 7.5 (m, 1H, Ar-H), 7.61 (s, 1H, Het-H), 7.79 (s, 1H, Het-H), 7.95 (s, 1H, Het-H).

FAB-MS: 553.1 (MH^+), calcd. $C_{28}H_{34}F_2N_8O_2$ 552.573.

Example 41

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(2-propyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

The title compound **41** was prepared by alkylation of triazolone **35** with 2-bromopropane in the presence of cesium carbonate following the procedure similar to the above described for example **36**.

Yield 80%.

m.p.: 166-167 °C.

^{1}H NMR ($CDCl_3$) δ: 0.97 (d, 3H, CH_3), 1.40 (d, 6H, 2XCH_3), 2.60 (m, 2H, CH2), 3.0 (m, 3H, CH_2 and CH), 3.22 (m, 4H, 2XCH_2), 4.55 (m, 1H, CH), 4.9 (AB q, 2H, CH2), 5.15 (s, 1H, OH), 6.7- 6.85 (m, 2H, Ar-H), 6.96 (d, 2H, Ar-H, J=9 Hz), 7.38 (d, 2H, Ar-H, J=9 Hz), 7.5 (m, 1H, Ar-H), 7.59 (s, 1H, Het-H), 7.79 (s, 1H, Het-H), 7.95 (s, 1H, Het-H).

FAB-MS: 539 (MH^+), calcd. $C_{27}H_{32}F_2N_8O_2$ 538.6.

Example 42

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(2-hydroxypropyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

To a mixture of triazolone **35** (248 mg, 0.5 mmol) and potassium carbonate (138 mg, 1 mmol) in DMF (6 ml), 1,2-epoxypropane (870 mg, 15 mmol) was added. The reaction mixture was heated at 60 °C for 18 h and concentrated in vacuo. The residue was treated with crushed ice, extracted with ethyl acetate (3 X 30 ml). The combined extract was washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting crude product was purified on a column of silica gel (EtOAc/MeOH, 9:1) to give the hydoxypropyltriazolone **42** as a colorless solid (200 mg, 72%).

m.p.: 110-112 °C (decomp).

^{1}H NMR ($CDCl_3$) δ : 0.97 (d, 3H, CH3), 1.28 (d, 3H, CH_3), 2.60 (m, 2H, CH_2), 2.9-3.1 (m and q merg d, 3H, CH_2 and CH), 3.23 (m, 4H, 2XCH_2), 3.7-4.0 (m,

2H, CH_2), 4.8-5.0 (AB q, 2H, CH2), 5.12 (s, 1H, OH), 6.65-6.85 (m, 2H, Ar-H), 6.96 (d, 2H, Ar-H, J=9 Hz), 7.37 (d, 2H, Ar-H, J=9 Hz), 7.5 (m, 1H, Ar-H), 7.63 (s, 1H, Het-H), 7.78 (s, 1H, Het-H), 7.94 (s, 1H, Het-H).

FAB-MS: 555.3 (MH^+), calcd. $C_{27}H_{32}F_2N_8O_3$ 554.60

tert-Butyl 4-(4-nitrophenyl)piperazine-1-carboxylate (XVII; X=H):

To a solution of 1-(nitrophenyl)piperazine (20.7, 0.1 mol) and triethylamine (21 ml) in dichloromethane (250 ml) at 0-5 °C was added dropwise a solution of di-*tert*-butyldicarbonate in dichloromethane (50 ml). The resulting mixture was stirred at 0-5 °C for 2 h and at room temperature for 18 h. Then the reaction mixture was diluted with 100 ml of chloroform, washed with water, brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue was triturated with hexane and hexane/ethyl acetate mixture to give the title compound as a yellow solid (29 g, 94%).

^{1}H NMR ($CDCl_3$) δ: 1.5 (s, 9H, $3XCH_3$), 3.43 (t, 4H, $2XCH_2$), 3.6 (t, 4H, $2XCH_2$), 6.8 (d, 2H, Ar-H, J=9 Hz), 8.15 (d, 2H, Ar-H, J=9 Hz).

tert-Butyl 4-(4-Aminophenyl)piperazine-1-carboxylate (XVIII; X=H):

A solution of butyl 4-(4-nitrophenyl)piperazine (60 g, 0.195 mol) in ethyl acetate (800 ml) was hydrogenated in the presence of 10% palldium on charcoal (6.0) at room temperature and 45 psi pressure in the Parr hydrogenator for 18 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give the title compound as a offwhite solid (50 g, 93%).

^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, 3XCH3), 3.0 (t, 4H, $2XCH_2$), 3.4 (br s, 2H, NH_2), 3.5 (t, 4H, $2XCH_2$), 6.65 (d, 2H, Ar-H), 6.85 (d, 2H, Ar-H).

tert-Butyl 4-(4-Phenoxycarbonylaminoph nyl)pip razine-1-carboxylate (XIX; X=H):

To a solution of *tert*-butyl 4-(4-aminoph nyl)piperazine-1-carboxylate (50 g, 0.18 mol) and triethylamine (39 ml, 0.27 mol) in dichloromethane (400 ml) was added dropwise a solution of phenyl chloroformate (36.65 g, 0.23 mol) in dichloromethane (100 ml) at 0 oC. The resulting reaction mixture was stirred for 2 h at 0 °C and additional 3 h at room temperature. Then diluted with chloroform (100 ml), washed with water, brine and dried over sodium sulphate. The solvent was removed under reduced pressure, the crude product was purified on a column of silica gel (hexane/EtOAc, 1:1) to give the tiltle compound as colorless solid (60 g, 84%).

m.p.: 158-160 °C.

^{1}H NMR ($CDCl_3$) δ: 1.48 (s, 9H, $3XCH_3$), 3.0-3.2 (m, 4H, $2XCH_2$), 3.6 (m, 4H, $2XCH_2$), 6.8 (brs, 1H, NH), 6.92 (d, 2H, Ar-H), 7.1-7.5 (complex, 7H, Ar-H).

4-[4-(4-*t*-BOC-piperazin-1-yl)phenylsemicarbazide (XX; X=H).

To a solution of *tert*-butyl 4-(phenoxycarbonylaminophenyl)piperazine-1-carboxylate (36 g, 90 mmol) in dimethoxyethane (300 ml), anhydrous hrazine (40 g, 1.25 mol) was added. The resulting reaction mixture was stirred at room temperature for 3-5 h. Solvent was removed under reduced pressure and the residue was treated with crushed ice and left overnight at room temperature. The precipitated solid was collected, washed with water and hexane to give the title compound as a offwhite solid (25 g, 82%).

^{1}H NMR ($CDCl_3$) δ: 1.48 (s, 9H, $3XCH_3$), 3.06 (t, 4H, $2XCH_2$), 3.58 (t, 4H, $2XCH_2$), 3.82 (s, 2H, NH2), 5.98 (s, 1H, NH), 6.89 (d, 2H, Ar-H, J=8.9 Hz), 7.36 (d, 2H, Ar-H, J=8.9 Hz), 7.95 (s, 1H, NH).

4[4-(4-*t*-BOC-Piperazin-1-yl)phenyl-2H-1,2,4-triazol-3-one (XXI; X=H):

A mixture of 4-[4-(4-t-BOC-piperazin-1-yl)phenylsemicarbazide (25 g, 75 mmol), formamidine acetate (31.2 g, 300 mmol) and triethylamin (50.5 ml,

360 mmol) in methoxyethanol (250 ml) was heated at 110 °C for 18 h. The solvent was removed under reduced pressure, the residue was treated with crushed ice and extracted with ethyl acetate (3X250 ml). Combined extract was successively washed with water and brine and dried over sodium sulphate. The solvent was removed under reduced pressure and the product was purified on a column of silica gel to give the title compound as a colorless solid (16.7 g, 65%).

m.p.: 195-197 °C.

^{1}H NMR ($CDCl_3$) δ: 1.48 (s, (H, 9H, $3XCH_3$), 3.16 (t, 4H, $2XCH_2$), 3.59 (t, 4H, $2XCH_2$), 6.98 (d, Ar-H, J=9 Hz), 7.38 (d, 2H, Ar-H), 7.62 (s, 1H, Het-H), 9.7 (brs, 1H, NH).

2-(3-Pentyl)-4[4-(4-*t*-BOC-piperazin-1-yl)phenyl-2H-1,2,4-triazol-3-one (XXII; X=H, R= 3-pentyl):

A mixture of 4[4-(4-*t*-BOC-piperazin-1-yl)phenyl-2H-1,2,4-triazol-3-one **XXI** (3.45 g, 10 mmol), 3-bromopentane (4.53 g) and potassium carbonate (2.76 g, 20 mmol) in DMF (30 ml) was heated at 80 °C for 18 h. The solvent was removed under reduced pressure, the residue was diluted with water, extracted with ethyl acetate (3X50 ml). The combined extract was washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. The resulting product was purified on a column of silica gel (2.9 g, 70%) to give the title compound as a colorless solid.

m.p.: 96-97 °C.

^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 6H, $2XCH_3$), 1.48 (s, 9H, $3XCH_3$), 1.7-1.9 (m, 4H, $2XCH_2$), 3.15 (t, 4H, $2XCH_2$), 3.59 (t, 4H, $2XCH_2$), 4.05 (m, 1H, CH), 6.98 (d, 2H, Ar-H, J=9 Hz), 7.44 (d, 2H, Ar-H, J=9 Hz), 7.63 (s, 1H, Het-H).

2-(3-Pentyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one (XXIII; X=H; R=3-pentyl):

To a solution of 2-(3-pentyl)-4-[4-(4-t-BOC-piperazin-1-yl)phenyl-1H-1,2,4-triazol-3-one (2.5 g, 6 mmol) in ethyl acetate (30 ml), 30 ml of 10% hydrochloric acid was added. The resulting heterogenious mixture was stirred at room temperature for 5 h. Solvent was removed under reduced pressure, the residue was diluted with water, basified with potassium carbonate and extracted with chloroform (3X50 ml). The combined extract was washed with water, brine, dried (Na_2SO_4) and concentrated to give the title compound as colorless solid (1.8 g, 95%).

m.p.: 135-137 °C.

^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 6H, $2XCH_3$), 1.7-1.9 (m, 4H, $2XCH_2$), 3.07 (m, 4H, $2XCH_2$), 3.18 (m, 4H, $2XCH_2$), 4.05 (m, 1H, CH), 6.95 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 7.63 (s, 1H, Het-H).

2-(2-Butyl)-4[4-(4-*t*-BOC-piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one (XXII; X=H, R=2-butyl):

The title compound was obtained by alkylation of triazolone **XXI** with 2-bromobutane in the presence of potassium carbonate.

m.p.: 134-135 °C.

^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3H, CH_3), 1.39 (d, 3H, CH_3), 1.48 (s, 9H, $3XCH_3$), 1.8 (m, 2H, CH2), 3.15 (t, 4H, $2XCH_2$), 3.59 (t, 4H, $2XCH_2$), 4.3 (m, 1H, CH), 6.97 (d, 2H, Ar-H, J=8.9 Hz), 7.42 (d, 2H, Ar-H, J=8.9 Hz), 7.61 (s, 1H, Het-H).

2-(2-Butyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one (XXIII; X=H, R=2-butyl):

The title compound was obtained by removal of *t*-BOC group of 2-(2-butyl)-4[4-(4-*t*-BOC-piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one with 3M hydrochloric acid.

m.p.: 91-93 °C.

^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3H, CH_3), 1.39 (d, 3H, CH_3), 3.04 (m, 4H, $2XCH_2$), 3.17 (m, 4H, $2XCH_2$), 4.29 (m, 1H, CH), 6.98 (d, 2H, Ar-H, J=8.9 Hz), 7.4 (d, 2H, Ar-H, J=8.9 Hz), 7.61 (s, 1H, Het-H).

4-[4-(4-t-BOC-Piperazin-1-yl)phenyl]-2-(2-propyl)-2H-1,2,4-triazol-3-one (XXII; X=H, R=2-propyl):

The title compound was obtained by alkylation of triazolone **XXI** with 2-bromopropane in the presence of potassium carbonate.

m.p: 166-167 °C.

^{1}H NMR ($CDCl_3$) δ: 1.41 (d, 6H, $2XCH_3$), 1.49 (s, 9H, $3XCH_3$), 3.16 (t, 4H, $2XCH_2$), 3.59 ($2XCH_2$), 4.55 (m, 1H, CH), 6.97 (d, 2H, Ar-H, J=8.9 Hz), 7.40 (d, 2H, Ar-H, J=8.9 Hz), 7.59 (s, 1H, Het-H).

4-[4-(Piperazin-1-yl)phenyl]-2-(2-propyl)-2H-1,2,4-triazol-3-one (XXIII; X=H, R=2-propyl): The title compound was obtained by removal of *t*-BOC group of 4-[4-(4-t-BOC-piperazin-1-yl)phenyl]-2-(2-propyl)-2H-1,2,4-triazol-3-one with 3M hydrochloric acid.

m.p.: 120-121 °C.

^{1}H NMR ($CDCl_3$) δ : 1.41 (d, 6H, $2XCH_3$), 3.04 (m, 4H, $2XCH_2$), 3.17 (m, 4H, $2XCH_2$), 4.55 (m, 1H, CH), 6.97 (d, 2H, Ar-H, J=9 Hz), 7.38 (d, 2H, Ar-H, J=9 Hz), 7.59 (s, 1H, Het-H).

2-(2-Hydroxypropyl)-4-[4-(4-t-BOC-piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one (XXII; X=H, R=2-hydroxypropyl):

The title compound was obtained by alkylation of triazolone **XXI** with 1,2-epoxypropane in the presence of potassium carbonate

m.p: 168-170 °C.

^{1}H NMR ($CDCl_3$) δ: 1.28 (d, 3H, CH_3), 1.48 (s, 9H, 3XCH_3), 3.17 (t, 4H, 2XCH_2), 3.4 (brs, 1H, OH), 3.59 (t, 4H, 2XCH_2), 3.70 (dd, 1H), 3.96 (dd, 1H), 4.2 (m, 1H, CH), 6.98 (d, 2H, Ar-H, J=8.9 Hz), 7.39 (d, 2H, Ar-H, J=8.9 Hz), 7.63 (s, 1H, Het-H).

2-(2-Hydroxypropyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one (XXIII; X=H, R=2-hydroxypropyl):

The title compound was obtained by removal of *t*-BOC group of 2-(2-hydroxypropyl)-4-[4-(4-*t*-BOC-piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one with 3M hydrochloric acid.

^{1}H NMR ($CDCl_3$) δ: 1.28 (d, 3H, CH_3), 3.0 (m, 4H, 2XCH_2), 3.2 (m, 4H, 2XCH_2), 3.8-4.0 (m, 2H, CH2), 4.2 (m, 1H, CH), 6.98 (d, 2H, Ar-H, J=9 Hz), 7.3 (d, 2H, Ar-H, J=9 Hz), 7.62 (s, 1H, Het-H)

Example 43

4-[4-(4-t-BOC-Piperazin-1-yl)phenyl]-2-[(4-trifluoromethyl)benzyl]-2H-1,2,4-triazol-3-one (XXII; X=H, R=4-trifluoromethylbenzyl):

The title compound was prepared by alkylation of triazolone **XXI** (X=H) with 4-(trifluoromethyl)benzyl bromide in the presence of potassium carbonate. After usual workup and purification on a column of silica gel, the title compound was obtained in 95% yield as a colorless solid.

^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, 3 x CH_3); 3.16 (t, 4H, 2 x $_2$); 3.59 (t, 4H, 2 x CH_2); 5.06 (s, 2H, CH_2); 6.98 (d, 2H, J = 8.9 Hz, Ar-H), 7.39 (d, 2H, J = 8.9 Hz, Ar-H); 7.5-7.60 (m, 6H, Ar-H); 7.64 (s, 1H, Het-H).

4-[4-(Piperazin-1-yl)phenyl]-2-[(4-trifluoromethyl)benzyl]-2H-1,2,4-triazol-3-one (XXIII; X=H, R=4-trifluoromethylb nzyl):

The title compound was obtained by removal of *t*-BOC group of 4-[4-(4-*t*-BOC-piperazin-1-yl)phenyl]-2-[(4-trifluoromethyl)benzyl]-2H-1,2,4-triazol-3-one with 3M hydrochloric acid. After usual workup the product was obtained as a colorless solid in 95% yield.

^{1}H NMR (DMSO-d_6) δ : 2.81-2.84 (m, 4H, 2 x CH_2); 3.04-3.07 (m, 4H, 2 x CH_2); 5.05 (s, 2H, CH_2); 7.0 (d, 2H, J = 9 Hz, Ar-H); 7.43-7.53 (m, 4H, Ar-H); 7.73 (d, 2H, J = 8 Hz, Ar-H); 8.38 (s, 1H, Het-H).

(2R,3R)-2-(2,4-Difluorophenyl) -1-(1H-1,2,4-triazol-1-yl)-3-[4-{4-[2-(4-trifluoromethylbenzyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl]}piperazin-1-yl]butan-2-ol (43):

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and piperazino compound **XXIII** (R= 4-trifluoromethylbenzyl; X=H) by following the similar procedure described for the example **36.**

Colorless solid, 189-191 °C, yield 65%.

^{1}H NMR ($CDCl_3$) δ: 0.98 (d, 3H, J = 5.5 Hz, CH_3), 2.57-2.63 (m, 2H, CH_2); 3.0-3.05 (m, 3H); 3.08 -3.23 (m, 4H, 2 x CH_2); 4.81-4.99 (q, 2H, CH_2); 5.07 (s, 2H, CH_2); 5.15 (s, 1H); 6.68-7.64 (m, 12H); 7.79 (s, 1H, Het-H); 7.95 (s, 1H, Het-H).

FAB-MS: 657.3 (MH^+) ; calcd. $C_{32}H_{31}O_2F_5N_8$ 656.64.

Example 44

4-[4-(4-*tert*-BOC-Piperazin-1-yl)phenyl]-2-(2,2,3,3-tetrafluoropropyl)-2H-1,2,4-triazol-3-one (XXII; X=H, R=2,2,3,3-tetrafluoropropyl):

The title compound was obtained by alkylation of triazolone **XXI** (X=H) with 2,2,3,3-tetrafluropropyl m thanesulphonat in th presence of potassium carbonate. The product was obtained as light yellow solid in quantitative yield.

^{1}H NMR ($CDCl_3$) δ: 1.48 (s, 9H, 3 x CH_3); 3.18 (t, 4H, 2 x CH_2); 3.59 (t, 4H, 2 x CH_2); 4.34-4.48 (m, 2H) 5.71-6.28 (m, 1H, CHF_2); 6.98 (d, 2H, Ar-H) 7.39 (d, 2H, Ar-H); 7.69 (s, 1H, Het-H).

4-[4-(Piperazin-1-yl)phenyl]-2-(2,2,3,3-tetrafluoropropyl)-2H-1,2,4-triazol-3-one (XXIII; X=H, R=2,2,3,3-tetrafluoropropyl):

The title compound was obtained by the deprotection of the BOC group of the above compound with 3N hydrochloric acid. The product was obtianed as light yellow solid in quantitative yield. This was used in the following step without further purification.

^{1}H NMR ($CDCl_3$) δ: 3.01-3.21 (m, 8H); 4.33-4.62 (m, 3H, CH_2 and N-H); 5.67-6.29 (m, 1H, CHF_2); 6.97 (d, 2H, Ar-H); 7.37 (d, 2H, Ar-H); 7.70 (s, 1H, Het-H).

2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(2,2,3,3-tetrafluoropropyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and piperazino compound **XXIII** (R=2,2,3,3,-tetrafluoropropyl; X=H) by following the similar procedure described for the example **36.**

Colorless solid, Yield 55%.

m.p: 155-157 °C.

^{1}H NMR ($CDCl_3$) δ: 0.97 (d, 3H, J = 5.4 Hz, CH_3); 2.57-2.65 (m, 2H, CH_2); 3.00-3.23 (m, 7H); 4.35-4.48 (m, 2H, CH_2); 4.82-5.00 (m, 2H, CH_2); 5.13 (s, 1H); 5.71-6.28 (m, 1H, -CHF_2); 6.69-6.83 (m, 2H, Ar-H); 6.96 (d, 2H, J = 9 Hz; Ar-H); 7.35-7.53 (m, 3H, Ar-H); 7.68 (s, 1H, Het-H); 7.79 (s, 1H, Het-H); 7.95 (s, 1H, Het-H).

FAB-MS: 611.2 (MH^+), calcd. $C_{27}H_{28}O_2F_6N_8$ 610.56.

Example 45

4-[4-(4-t-BOC-Piperazin-1-yl)phenyl]-2-(2,2,2-trifluoroethyl)-2H-1,2,4-triazol-3-one (XXII; X=H, R=2,2,2-trifluoroethyl):

The title compound was prepared from the reaction of triazolone **XXI** (X=H) with 2,2,2-trifluroethyl bromide in a sealed vessel in the presence of potassium carbonate. After usual workup and purification on a column of silica gel, the alkylated compound was obtained as a colorless solid in 21% yield.

^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, 3 x CH_3); 3.18 (t, 4H, 2 x CH_2); 3.59 (t, 4H, 2 x CH_2); 4.44 (q, 2H, CH_2); 6.98 (d, 2H, J = 7 Hz, Ar-H); 7.38 (d, 2H, J = 7 Hz, Ar-H); 7.69 (s, 1H, Het-H).

4-[4-(Piperazin-1-yl)phenyl]-2-(2,2,2-trifluoroethyl)-2H-1,2,4-triazol-3-one (XXIII; X=H, R=2,2,2-trifluoroethyl):

The title compound was obtained by deprotection of BOC group of the above compound with 3M hydrochloric acid.

^{1}H NMR ($CDCl_3$) δ: 1.73 (s, 1H, N-H); 3.00-3.20 (m, 8H, 4 x CH_2); 4.44 (q, 2H, CH_2); 6.95-7.00 (m, 2H, Ar-H); 7.34-7.39 (m, 2H, Ar-H); 7.68 (s, 1H, Het-H).

(2R,3R)-2-(2,4-Difluorophenyl) -1-(1H-1,2,4-triazol-1-yl)-3-[4-{4-[2-(2,2,2--trifluoroethyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl]}piperazin-1-yl]butan-2-ol.

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and piperazino compound **XXIII** (R= 2,2,2-trifluoroethyl, X=H) by following the similar procedure described for the example **36.**

Colorless solid, yield: 59%.
m.p: 95-97 °C.

^{1}H NMR ($CDCl_3$) δ: 0.90 (d, 3H, J = 6.3 Hz, CH_3); 2.50-2.56 (m, 2H, CH_2); 2.93-3.16 (m, 7H); 4.37 (q, 2H, CH_2); 4.83 (m, 2H, CH_2); 6.61-6.91 (m, 4H, Ar-H); 7.27-7.46 (m, 3H, Ar-H); 7.61 (s, 1H, Het-H); 7.71 (s, 1H, Het-H); 7.88 (s, 1H, Het-H).

FAB-MS : 579.2 (MH^+), calcd. $C_{26}H_{27}O_2F_5N_8$ 578.55.

Example 46

2-(2,4-Difluorobenzyl)-4-[4-(4-*tert*-BOC-piperazin-1-yl)-2H-1,2,4-triazol-3-one (XXII; X=H, R=2,4-difluorobenzyl):

The title compound was prepared by alkylation of triazolone **XXI** (X=H) with 2,4-difluorobenzyl bromide in the presence of potassium carbonate. After usual workup the product was obtained in quantitative yield as a colorless solid.

^{1}H NMR ($CDCl_3$) δ : 1.49 (3, 9H, 3 x CH_3); 3.17 (t, 4H, 2 x CH_2); 3.59 (t, 4H, 2 x CH_2); 5.04 (s, 2H, CH_2); 6.78-7.01 (m, 4H, Ar-H); 7.29-7.45 (m, 3H, Ar-H); 7.63 (s, 1H, Het-H).

2-(2,4-Difluorobenzyl)-4-[4-(4-piperazin-1-yl)-2H-1,2,4-triazol-3-one (XXIII; X=H, R=2,4-difluorobenzyl):

The title compound was obtained by deprotection of BOC group of the above compound with 3N hydrochloric acid.

Colorless solid, 70% yield.

^{1}H NMR $_3$) δ: 1.70 (s, 1H, N-H); 2.92-3.10 (m, 8H, 4 x CH_2); 4.96 (s, 2H, CH_2); 6.71-6.91 (m, 4H, Ar-H); 7.21-7.37 (m, 3H, Ar-H); 7.54 (s, 1H, Het-H).

(2R,3R)-3-[4-{4-[2-(2,4-Difluorobenzyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl]}piperazin-1-yl] -2-(2,4-difluorophenyl) -1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane and piperazino compound **XXIII** (R= 2,4-difluorobenzyl, X=H) by following the similar procedure described for the example **36.**

Colorless solid, yield 53%

m.p.: 161-163 °C.

^{1}H NMR ($CDCl_3$) δ: 0.91 (d, 3H, J = 5.6 Hz, CH_3); 2.49-2.57 (m, 2H, CH_2); 2.91-3.14 (m, 7H); 4.73-4.91 (m, 2H, CH_2); 4.97 (s, 2H, CH_2); 5.09 (s, 1H); 6.60-6.90 (m, 6H, Ar-H); 7.25-7.45 (m, 4H, Ar-H); 7.54 (s, 1H, Het-H); 7.70 (s, 1H, Het-H); 7.87 (s, 1H, Het-H).

FAB-MS: 623.1 (MH^+); calcd. $C_{30}H_{30}F_4O_2N_8$ 622.63.

Example 47

4-[4-(4-*tert*-BOC-Piperazin-1-yl)phenyl-2-(4-trifluoromethoxy)benzyl-2H-1,2,4-triazol-3-one (XXII; X=H, R=4-trifluoromethoxybenzyl):

The title compound was prepared by alkylation of triazolone **XXI** (X=H) with 4-(trifluoromethoxy)benzyl bromide in the presence of potassium carbonate. After usual workup the product was obtained in 90% yield as a colorless solid.

^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, 3 x CH_3), 3.13-3.18 (m, 4H, 2 x CH_2); 3.56-3.61 (m, 4H, 2 x CH_2); 5.00 (s, 2H, CH_2); 6.94-6.99 (m, 2H, Ar-H); 7.17-7.22 (m, 2H, Ar-H) 7.38-7.47 (m, 4H, Ar-H); 7.63 (s, 1H, Het-H).

4-[4-(Piperazin-1-yl)phenyl-2-(4-trifluoromethoxy)benzyl-2H-1,2,4-triazol-3-one (XXIII; X=H, R=4-trifluoromethoxybenzyl):

The title compound was obtained by removal of *t*-BOC group of the aboove compound with 3M hydrochloric acid.

Colorless solid, quantitative yield.

^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 1H, N-H); 3.01-3.20 (m, 8H, 4 x CH_2); 5.01 (s, 2H, CH_2); 6.95-6.99 (m, 2H, Ar-H); 7.18-7.22 (m, 2H, Ar-H), 7.34-7.47 (m, 4H, Ar-H); 7.61 (s, 1H, Het-H).

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(4-trifluoromethoxybenzyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane and piperazino compound **XXIII** [R=4-(trifluoromethoxy)benzyl; X=H] by following the similar procedure described for the example **36.**

Colorless solid, 91% yield

m.p.: 175-177 °C.

^{1}H NMR ($CDCl_3$) δ: 0.98 (d, 3H, J = 5.7 Hz, CH_3); 2.57-2.65 (m, 2H, CH_2); 2.99-3.22 (m, 7H); 4.82-4.92 (m, 2H, CH_2) 5.01 (s, 2H, CH_2); 5.15 (s, 1H); 6.68-7.54 (m, 11H, Ar-H); 7.62 (s, 1H, Het-H); 7.79 (s, 1H, Het-H); 7.95 (s, 1H, Het-H).

FAB-MS: 671.3 (MH^+), calcd. $C_{32}H_{31}O_3F_5N_8$ 670.64.

Example 48

2-(4-Methoxybenzyl)-4-[4-(4-*tert*-BOC-piperazin-1-yl)phenyl-2H-1,2,4-triazol-3-one (XXII; X=H, R=4-methoxybenzyl):

The title compound was prepared by alkylation of triazolone **XXI** (X=H) with 4-methoxybenzyl bromide in DMF in the presence of potassium carbonate.

Colorless solid, 96% yield.

^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, 3 x CH_3); 3.12-3.17 (m, 4H, 2 x CH_2); 3.55-3.61 (m, 4H, 2 x CH_2); 3.77 (s, 3H, OCH_3); 4.94 (s, 2H, CH_2); 6.83-6.99 (m, 4H, Ar-H); 7.32-7.41 (m, 4H, Ar-H); 7.59 (s, 1H, Het-H).

2-(4-Methoxybenzyl)-4-[4-(piperazin-1-yl)phenyl-2H-1,2,4-triazol-3-one (XXIII; X=H, R=4-methoxybenzyl):

The title compound was obtained by deprotection of *t*-BOC group of 2-(4-methoxybenzyl)-4-[4-(4-*tert*-BOC-piperazin-1-yl)phenyl-2H-1,2,4-triazol-3-one with 3M hydrochloric acid.

Colorless solid, 94% yield.

^{1}H NMR ($CDCl_3$) δ: 1.62 (s, 1H, N-H); 3.01-3.19 (m, 8H, 4 x CH_2); 3.79 (s, 3H, OCH_3); 4.95 (s, 2H, CH_2); 6.86-6.99 (m, 4H, Ar-H); 7.35-7.39 (m, 4H, Ar-H); 7.57 (s, 1H, Het-H).

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(4-methoxybenzyl)-2H-1,2,4 -triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and piperazino compound **XXIII** (R= 4-methoxybenzyl; X=H) by following the similar procedure described for the example **36**.

Colorless solid, yield 69%.

m.p. 178-179 °C

^{1}H NMR ($CDCl_3$) δ: 0.96 (d, 3H, J = 6.8 Hz, CH_3); 2.56-2.62 (m, 2H CH_2); 2.99-3.21 (m, 7H); 3.79 (s, 3H, OCH_3); 4.89-4.99 (m, 2H, $_2$); 4.95 (s, 2H, CH_2); 5.14 (s, 1H); 6.68-6.97 (m, 6H, Ar-H); 7.35-7.53 (m, 5H, Ar-H), 7.58 (s, 1H, Het-H); 7.78 (s, 1H, Het-H); 7.95 (s, 1H, Het-H).

FAB-MS: 617.0 (MH^+), calcd. $C_{32}H_{34}O_3F_2N_8$ 616.67.

Exampl 49

2-(2,4-Bis-trifluoromethyl)benzyl-4-[4-(4-*tert*-BOC-piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one (XXII; X=H, R=2,4-bis-trifluoromethylbenzyl):

The title compound was prepared by alkylation of triazolone **XXI** (X=H) with 2,4-bis(trifluoromethyl)benzyl bromide in the presence of potassium carbonate. After usual workup the product was obtained in 76% yield as a colorless solid.

^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, 3 x CH_3); 3.15-3.20 (m, 4H, 2 x CH_2); 3.57-3.63 (m, 4H, 2 x CH_2); 5.31 (s, 2H, CH_2); 6.98-7.02 (m, 2H, Ar-H); 7.40-7.53 (m, 3H, Ar-H); 7.72 (s, 1H, Het-H); 7.77-7.95 (m, 2H, Ar-H).

2-(2,4-Bis-trifluoromethyl)benzyl-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one (XXIII; X=H, R=2,4-bis-trifluoromethylbenzyl):

The title compound was obtained by deprotection of *t*-BOC group of 4[-4-(4-*tert*-BOC-piperazin-1-yl)phenyl]-2-(2,4-*bis*-trifluoromethyl)benzyl-2H-1,2,4-triazol-3-one with 3M hydrochloric acid.

Colorless solid, 91% yield.

^{1}H NMR ($CDCl_3$) δ: 1.88 (s, 1H, NH); 3.02-3.21 (m, 8H, 4 x CH_2); 5.31 (s, 2H, CH_2); 6.96-7.01 (m, 2H, Ar-H); 7.39-7.95 (m, 5H, Ar-H); 7.70 (s, 1H, Het-H).

(2R,3R)-3-[4-{4-[2-(2,4-Bis-trifluoromethylbenzyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-2-(2,4-difluorophenyl) -1-(1H-1,2,4-triazol-1-yl)-butan-2-ol:

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and piperazino compound **XXIII** [R= 2,4-bis(trifluromethyl)benzyl; X=H] by following the similar procedure d scribed for the xample **36.**

Colorless solid, yield: 70%.

m.p.: 146-148 °C.

^{1}H NMR ($CDCl_3$) δ: 0.99 (d, 3H, J = 6.8 Hz, CH_3); 2.58-2.66 (m, 2H, CH_2); 3.01-3.24 (m, 7H); 4.82-5.00 (m, 2H, CH_2); 5.14 (s, 1H); 5.31 (s, 2H, CH_2), 6.69-6.83 (m, 2H, Ar-H); 6.96-7.00 (m, 2H, Ar-H) 7.40-7.53 (m, 4H, Ar-H); 7.72 (s, 1H, Het-H) 7.77-7.81 (m, 2H, Ar-H & Het-H); 7.95 (s, 2H, Ar-H & Het-H).

FAB-MS: 723 (MH^+), calcd. 722.64.

Example 50

4-[4-(4-*tert*-BOC-Piperazin-1-yl)phenyl]-2-[4-(2,2,3,3-tetrafluoropropoxy)benzyl]-2H-1,2,4-triazol-3-one [XXII; X=H, R=4-(2,2,3,3-tetrafluoropropoxy)benzyl];

The title compound was prepared by alkylation of triazolone **XXI** (X=H) with 4-(2,2,3,3-tetrafluoropropoxy)benzyl bromide in the presence of potassium carbonate. After usual workup the product was obtained in 81% yield as a colorless solid.

^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, 3XCH_3), 3.12-3.17 (m, 4H, 2XCH2), 3.55-3.60 (m, 4H, 2XCH_2), 4.26-4.37 (m, 2H, OCH_2), 4.94 (s, 2H, CH_2), 5.76-6.36 (m, 1H, CF_2H), 6.86-6.98 (m, 4H, Ar-H), 7.37 (m, 4H, Ar-H), 7.60 (s, 1H, Het-H).

4-[4-(Piperazin-1-yl)phenyl]-2-[4-(2,2,3,3-tetrafluoropropoxy)benzyl]-2H-1,2,4-triazol-3-one [XXIII; X=H, R=4-(2,2,3,3-tetrafluoropropoxy)benzyl];

The title compound was obtained by deprotection of *t*-BOC group of the above compound with 3M hydrochloric acid. After usual workup the product was obtained in 98% yield as colorless solid.

^{1}H NMR ($CDCl_3$) δ: 1.87 (s, 1H, NH), 3.01-3.19 (m, 8H, 4XCH_2), 4.27-4.39 (m, 2H, OCH_2), 4.96 (s, 2H, CH_2), 5.77-6.35 (m, 1H, CF_2H), 6.89-6.99 (m, 4H, Ar-H), 7.33-7.42 (m, 4H, Ar-H), 7.58 (s, 1H, Het-H).

(2R,3R)-2-(2,4-Difluoroph nyl)-3-[4-{4-[2-((4-(2,2,3,3-tetrafluoropropoxy)benzyl))-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and piperazino compound **XXIII** [R=4-(2,2,3,3-tetrafluoropropoxy)benzyl; X=H] by following the similar procedure described for the example **36.**

Yield 86%, colorless prisms.

m.p.: 83-85 °C.

^{1}H NMR($CDCl_3$) δ: 0.97 (d, 3H, CH_3), 2.57-2.62 (m, 2H, $_2$), 2.99-3.22 (m, 7H), 4.27-4.38 (m, 2H, CH_2), 4.81-4.99 (m, 2H, CH_2), 4.96 (s, 2H, CH_2), 5.15 (s, 1H, OH), 5.77-6.35 (m, 1H, CF_2H), 6.68-6.98 (m, 6H, Ar-H), 7.35-7.53 (m, 5H, Ar-H), 7.59 (s, 1H, Het-H), 7.78 (s, 1H, Het-H), 7.95 (s, 1H, Het-H).

FAB-MS: 717.3 (MH^+), calcd $C_{34}H_{34}F_6O_3N_8$ 716.69.

Example 51

4-[3-Fluoro-4-(4-*tert*-BOC-piperazin-1-yl)phenyl]-2-[4-(trifluoromethyl)benzyl]-2H-1,2,4-triazol-3-one (XXII; X=F, R=4-trifluoromethylbenzyl):

The title compound was prepared by alkylation of triazolone **XXI** (X=F) with (trifluoromethyl)benzyl bromide in the presence of potassium carbonate. After usual workup and purification on a column of silica gel, the title compound was obtained in 95% yield as a colorless solid.

^{1}H NMR ($CDCl_3$) δ: 1.48 (s, 9H, $3XCH_3$), 3.04 (m, 4H, $2XCH_2$), 3.60 (m, 4H, $2XCH_2$), 5.06 (s, 2H, CH_2), 6.99 (m, 1H, Ar-H), 7.2-7.4 (m, 2H, Ar-H), 7.49-7.62 (m, 4H, Ar-H), 7.64 (s, 1H, Het-H).

4-[3-Fluoro-4-(piperazin-1-yl)phenyl]-2-[4-(trifluoromethyl)benzyl]-2H-1,2,4-triazol-3-one (XXIII; X=F, R=4-trifluoromethylbenzyl):

The title compound was obtained in 96% yield by deprotection of BOC group of the above compound with 3M hydrochloric acid.

^{1}H NMR ($CDCl_3$) δ: 3.0 (s, 8H, 4XCH_2), 5.05 (s, 2H, CH_2), 7.0 (m, 1H, Ar-H), 7.2-7.38 (m, 2H, Ar-H), 7.48-7.62 (m, 4H, Ar-H), 7.65 (s, 1H, Het-H).

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{3-fluoro-4-[2-(4-trifluoromethyl)benzyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol:

The title compound was prepared from (2R,3S)-2-(2,4-difluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane **IV** and piperazino compound **XXIII** [R = 4-(trifluoromethyl)benzyl; X=F] by following the similar procedure described for the example **36.**

Colorless solid, Yield 69%.

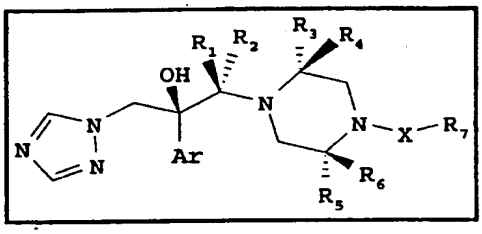
m.p.: 189-191 °C.

^{1}H NMR ($CDCl_3$) δ: 0.99 (d, 3H, CH_3), 2.65 (m, 2H, CH_2), 2.95-3.2 (m, 7H, 3XCH_2 and CH), 4.90 (AB q, 2H, CH_2), 5.07 (s, 2H, CH_2), 5.15 (s, 1H, OH), 6.7-6.85 (m, 2H, Ar-H), 7.04 (m, 1H, Ar-H), 7.2-7.62 (m, 7H, Ar-H), 7.64 (s, 1H, Het-H), 7.79 (s, 1H, Het-H), 7.95 (s, 1H, Het-H).

FAB-MS: 673.8 (MH^+), calcd. $C_{32}H_{30}F_6N_8O_2$ 672.634

W claim:

1. A compound of formula I, or an optical isomer or pharmaceutically acceptable salt thereof,



I

wherein:

Ar is a phenyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, CF_3 and OCF_3;

R_1 and R_2 are each independently hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, with the proviso that where R_1 is hydrogen, R_2 is other than hydrogen, and vice versa;

R_3 and R_4 are each independently hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, or R_3 and R_4 together form =S;

R_5 and R_6 are each independenly hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, or R_5 and R_6 together form =S;

X is selected from the group consisting of a direct bond, CO, CS, SO_2 and -N=N-;

R_7 is selected from the group consisting of

i) hydrogen,

ii) CN

iii) CHO

iv) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) C_1-C_4 alkoxy, (3) halogen, (4) formyl, (5) carboxyl, (6) C_1-C_4 acyloxy, (7) C_1-C_4 alkoxycarbonylamino, (8) phenyl- or naphthyl-oxycarbonylamino, (9) semicarbazido, (10) formamido, (11) thioformamido, (12) hydroxy, (13) nitro, (14) amino, (15) furyl, (16) triazolyl, (17) thienyl, (18) oxazolyl, (19) imidazolyl and (20) triazolone-yl,

v) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-4 heteroatoms each independently selected from the group consisting of N, O and S, which heterocycle is unsubstituted or ring-substituted with 1-3 substituents each independently selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) benzyl which is unsubstituted or substituted with 1-3 substituents selected from the group consisting of C_1-C_4 alkyl, CF_3, halogen and OCF_3, (3) halogen, (4) hydroxy, (5) nitro, (6) amino, (7) C_1-C_4 acylamino, (8) formyl, (9) formamido, (10) thioformamido, (11) C_1-C_4 alkoxycarbonylamino, (12) phenyl- or naphthyl-oxycarbonylamino and (13) semicarbazido,

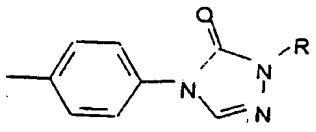
vi) NHR_8 wherein R_8 is selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently s lected from th group consisting of halog n, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f)

C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl and (t) triazolone-yl, and (3) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of hydroxy, halogen, amino and carboxyl,

vii) OR_9 wherein R_9 is selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f) C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl and (t) triazolone-yl and (3) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4

alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (c) naphthyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (d) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, (e) (C_1-C_4 alkyl)phenyl, (f) (C_1-C_4 alkyl)naphthyl, (g) hydroxy, (h) halogen, (i) amino and (j) carboxyl, and

viii) a group of the formula



wherein R is selected from the group consisting of (1) hydrogen, (2) C_1-C_{10} alkyl which is unsubstituted or substituted by 1-5 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (3) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of

halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f) C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl, (t) triazolone-yl, (u) CF_3 and (v) OCF_3, (4) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (c) naphthyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (d) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, (e) (C_1-C_4 alkyl)phenyl, (f) (C_1-C_4 alkyl)naphthyl, (g) hydroxy, (h)

halogen, (i) amino and (j) carboxyl, (5) phenyl(C_1-C_4 alkyl) which is unsubstituted or ring-substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_5 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) halogen, (c) halo(C_1-C_4 alkyl), (d) C_1-C_4 alkoxy, (e) hydroxy, (f) amino, (g) carboxyl, (h) trifluormethoxyl, (i) trifluoromethyl, (j) tetrafluoroethyl, (k) tetrafluoroethoxyl, (l) tetrafluoropropyl and (m) tetrafluoropropoxyl, (6) naphthyl(C_1-C_4 alkyl) which may be substituted with 1-6 substituents selected from (a) C_1-C_5 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) halogen, (c) (C_1-C_4 alkyl)halo, (d) C_1-C_4 alkoxy, (e) hydroxy, (f) amino, (g) carboxyl, (h) trifluormethoxyl, (i) trifluoromethyl, (j) tetrafluoroethyl, (k) tetrafluoroethoxyl, (l) tetrafluoropropyl and (m) tetrafluoropropoxyl, (7) methoxyl, (8) trifluormethoxyl, (9) trifluoromethyl, (10) trifluoroethyl, (11) tetrafluoroethyl, (12) tetrafluoroethoxyl, (13) tetrafluoropropyl and (14) tetrafluoropropoxyl.

2. The compound according to claim 1, wherein Ar is selected from the group consisting of 4-fluorophenyl, 2-4-difluorophenyl, 2,4,6-trifluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2,4,6-trichlorophenyl, 4-trifluoromethylphenyl and 4-trifluoromethoxyphenyl.

3. The compound according to claim 1, wherein Ar is a phenyl group having 1 to 2 substituents each independently selected from the group consisting of fluorine, chlorine, trifluoromethyl and trifluromethoxy.

4. The compound according to claim 1, wherein Ar is selected from the group consisting of 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-trifluromethylphenyl and 4-trifluorom thoxyphenyl.

5. The compound according to claim 1, wherein Ar is 2,4-diflourophenyl.

6. The compound according to claim 1, wherein R_1 is alkyl.

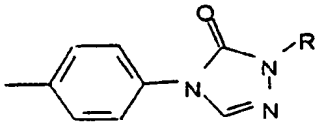
7. The compound according to claim 1, wherein R_1 is methyl.

8. The compound according to claim 1, wherein R_2 is hydrogen.

9. The compound according to claim 1, wherein R_1 and R_2 are the same, and the compound has a 2R isomeric configuration.

10. The compound according to claim 1, wherein R_1 and R_2 are different, and the compound has a 2R, 3R isomeric configuration.

11. The compound according to claim 1, wherein X is a direct bond and R_7 is a group of the formula



12. The compound according to claim 11, wherein Ar is 2,4-difluorophenyl, R_1 is methyl, and R_2 through R_6 are each hydrogen.

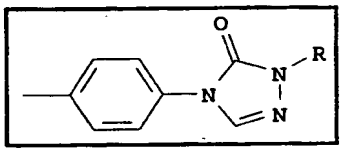
13. The compound according to claim 1, wherein R_1 is hydrogen and R_2 is methyl.

14. The compound according to claim 1, wherein R_3 through R_6 are each hydrogen.

15. The compound according to claim 1, wherein R_3 and R_5 are each methyl and R_4 and R_6 are each hydrogen.

16. The compound according to claim 1, wherein X is a direct bond.

17. The compound according to claim 1, wherein R_7 is group of the formula



wherein R is selected from the group consisting of 2-propyl, 2-butyl, 3-pentyl, 2-hydroxypropyl, 4-trifluoromethylbenzyl, tetrafluoropropyl, trifluoroethyl, 2,4-difluorobenzyl, 4-methoxybenzyl, 4-trifluoromethoxybenzyl and 2,4-bis(trifluoromethyl)benzyl.

18. The compound according to claim 1, wherein the compound is selected from the group consisting of:

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-ethoxycarbonylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Diflurophenyl)-3-(piperazin-1-yl)-1-(1H-1,2,4-triazole-1-yl)butan-2-ol,

(2R,3R)-3-(4-Cyanopiperazin-1-yl)-2-(2,4-diflurophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Diflurophenyl)-3-(4-formylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-(2,5-dimethylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-(2,5-dimethyl-4-thoxycarbonylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-(4-*tert*-BOC-Piperazin-1-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-(Anilinocarbonylpiperazin-1-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-ethylaminocarbonylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-(Anilinothiocarbonylpiperazin-1-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-ethylaminothiocarbonylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-[4-(2,4-Difluorobenzoyl)piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-[4-(4-trifluoromethylbenzoyl)piperazin-1-yl]butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-nitrobenzoyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-[4-(4-Aminobenzoyl)piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(*p*-toluenesulphonyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(methanesulphonyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-nitrophenylsulphonyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-[4-(4-Aminophenylsulphonyl)piperazin-1-yl]- 2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(3-azo-1H-1,2,4-triazol-3-yl))piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(2-thiazolyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(1H-1,2,4-triazol-3-yl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(1H-5-tetrazolyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[2-(4-*tert*-butylbenzyl)-2H-tetrazol-5-yl]piperazin-1-yl}-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-{4-[2-(4-trifluoromethylbenzyl)-2H-tetrazol-5-yl]piperazin-1-yl}butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[2-(4-*tert*-butylbenzyl)-2H-1,2,4-triazol-3-yl]piperazin-1-yl}-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[1-(4-*tert*-butylbenzyl)-1H-1,2,4-triazol-3-yl]piperazin-1-yl}-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-{4-[1-(4-trifluoromethylbenzyl)-1H-1,2,4-triazol-3-yl]piperazin-1-yl}butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-(4-phenylpiperazin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-nitrophenyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-[4-(4-Aminophenyl)piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-ethoxycarbonylaminophenyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-(4-phenoxycarbonylaminophenyl)piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-{4-[4-(semicarbazid-4-yl)phenyl]piperazin-1-yl}-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, and

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-{4-[4-(2H-1,2,4-triazol-3-one-4-yl)phenyl]piperazin-1-yl}butan-2-ol.

19. The compound according to claim 1, wherein the compound is selected from the group consisting of:

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2S,3S)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3S)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(3-pentyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-3-[4-{4-[2-(2-Butyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(2-propyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(2-hydroxypropyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-[4-{4-[2-(4-trifluoromethyl)benzyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(2,2,3,3-tetrafluoro)propyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)- butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-[4-{4-[2-(2,2,2-trifluoro)ethyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]butan-2-ol,

(2R,3R)-3-[4-{4-[2-(2,4-Difluorobenzyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(4-trifluoromethoxy)benzyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(4-methoxylbenzyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,

(2R,3R)-3-[4-{4-[2-(2,4-Bis-trifluoromethylbenzyl)-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-((4-(2,2,3,3-tetrafluoropropoxy)benzyl))-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, and

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{3-fluoro-4-[2-(4-trifluoromethyl)benzyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

20. The compound according to claim 19, wherein the compound is selected from the group consisting of:

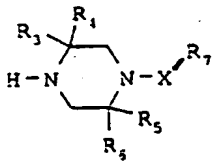
(2R,3R)-2-(2,4-Difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-[4-{4-[2-(4-trifluoromethyl)benzyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-(4-trifluoromethoxy)benzyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{4-[2-((4-(2,2,3,3-tetrafluoropropoxy)benzyl))-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol, and

(2R,3R)-2-(2,4-Difluorophenyl)-3-[4-{3-fluoro-4-[2-(4-trifluoromethyl)benzyl-2H-1,2,4-triazol-3-one-4-yl]phenyl}piperazin-1-yl]-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

21. A compound of formula III,



III

wherein:

R_3 and R_4 are each independently hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, or R_3 and R_4 together form =Z, wherein Z is oxygen or sulphur;

R_5 and R_6 are each independenly hydrogen or C_1-C_4 alkyl group which is unsubstituted or substituted by 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, or R_5 and R_6 together form =Z, wherein Z is oxygen or sulphur;

X is selected from the group consisting of a direct bond, CO, CS, SO_2 and -N=N-;

R_7 is selected from the group consisting of

i) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) C_1-C_4 alkoxy, (3) halogen, (4) formyl, (5) carboxyl, (6) C_1-C_4 acyloxy, (7) C_1-C_4 alkoxycarbonylamino, (8) phenyl- or naphthyl-oxycarbonylamino, (9) semicarbazido, (10) formamido, (11) thioformamido, (12) hydroxy, (13) nitro, (14) amino, (15) furyl, (16) triazolyl, (17) thienyl, (18) oxazolyl, (19) imidazolyl and (20) triazolone-yl,

ii) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-4 heteroatoms each independently selected from the group consisting of N, O and S, which heterocycle is unsubstituted or ring-substituted with 1-3 substituents each independently selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substitut d with 1-3

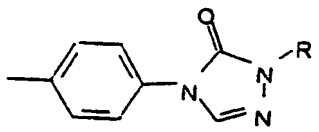
substituents each independently select d from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) benzyl which is unsubstituted or substituted with 1-3 substituents selected from the group consisting of C_1-C_4 alkyl, CF_3, halogen and OCF_3, (3) halogen, (4) hydroxy, (5) nitro, (6) amino, (7) C_1-C_4 acylamino, (8) formyl, (9) formamido, (10) thioformamido, (11) C_1-C_4 alkoxycarbonylamino, (12) phenyl- or naphthyl-oxycarbonylamino and (13) semicarbazido,

iii) NHR_8 wherein R_8 is selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f) C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl and (t) triazolone-yl, and (3) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of hydroxy, halogen, amino and carboxyl,

iv) OR_9 wherein R_9 is selected from the group consisting of (1) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (2) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f)

C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl and (t) triazolone-yl and (3) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (c) naphthyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (d) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, (e) (C_1-C_4 alkyl)phenyl, (f) (C_1-C_4 alkyl)naphthyl, (g) hydroxy, (h) halogen, (i) amino and (j) carboxyl, and

v) a group of the formula



wherein R is selected from the group consisting of (1) hydrogen, (2) C_1-C_{10} alkyl which is unsubstituted or substituted by 1-5 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (3) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) C_1-C_4 alkoxy, (c) halogen, (d) formyl, (e) carboxyl, (f) C_1-C_4 acyloxy, (g) C_1-C_4 alkoxycarbonylamino, (h) phenyl- or naphthyl-oxycarbonylamino, (i) semicarbazido, (j) formamido, (k) thioformamido, (l) hydroxy, (m) nitro, (n) amino, (o) furyl, (p) triazolyl, (q) thienyl, (r) oxazolyl, (s) imidazolyl, (t) triazolone-yl, (u) CF_3 and (v) OCF_3, (4) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) phenyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L)

hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (c) naphthyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of (A) C_1-C_4 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (B) C_1-C_4 alkoxy, (C) halogen, (D) formyl, (E) carboxyl, (F) C_1-C_4 acyloxy, (G) C_1-C_4 alkoxycarbonylamino, (H) phenyl- or naphthyl-oxycarbonylamino, (I) semicarbazido, (J) formamido, (K) thioformamido, (L) hydroxy, (M) nitro, (N) amino, (O) furyl, (P) triazolyl, (Q) thienyl, (R) oxazolyl, (S) imidazolyl and (T) triazolone-yl, (d) a 5- or 6-membered monocyclic or 8- to 10-membered bicyclic heterocycle having 1-3 heteroatoms each independently selected from the group consisting of N, O and S, (e) (C_1-C_4 alkyl)phenyl, (f) (C_1-C_4 alkyl)naphthyl, (g) hydroxy, (h) halogen, (i) amino and (j) carboxyl, (5) phenyl(C_1-C_4 alkyl) which is unsubstituted or ring-substituted with 1-3 substituents each independently selected from the group consisting of (a) C_1-C_5 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) halogen, (c) halo(C_1-C_4 alkyl), (d) C_1-C_4 alkoxy, (e) hydroxy, (f) amino, (g) carboxyl, (h) trifluormethoxyl, (i) trifluoromethyl, (j) tetrafluoroethyl, (k) tetrafluoroethoxyl, (l) tetrafluoropropyl and (m) tetrafluoropropoxyl, (6) naphthyl(C_1-C_4 alkyl) which may be substituted with 1-6 substituents selected from (a) C_1-C_5 alkyl which is unsubstituted or substituted with 1-3 substituents each independently selected from the group consisting of halogen, hydroxy, C_1-C_4 alkoxy and amino, (b) halogen, (c) (C_1-C_4 alkyl)halo, (d) C_1-C_4 alkoxy, (e) hydroxy, (f) amino, (g) carboxyl, (h) trifluormethoxyl, (i) trifluoromethyl, (j) tetrafluoroethyl, (k) tetrafluoroethoxyl, (l) tetrafluoropropyl and (m) tetrafluoropropoxyl, (7) methoxyl, (8) trifluormethoxyl, (9) trifluoromethyl, (10) trifluoroethyl, (11) tetrafluoroethyl, (12) tetrafluoroethoxyl, (13) tetrafluoropropyl and (14) tetrafluoropropoxyl.

22. The compound according to claim 21, wherein th compound is selected from the group consisting of:

2-(4-*tert*-butylbenzyl)-5-(piperazin-1-yl)-2H-tetrazole,

5-(piperazin-1-yl)-2-[4-(trifluoromethyl)benzyl]-2H-tetrazole

2-(4-*tert*-butylbenzyl)-3-(piperazin-1-yl)-2H-1,2,4-triazole,

1-(4-*tert*-butylbenzyl)-3-(piperazin-1-yl)-1H-1,2,4-triazole,

3-(piperazin-1-yl)-2-[4-(trifluoromethyl)benzyl]-2H-1,2,4-triazole,

2-(3-pentyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one,

2-(2-butyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one,

4-[4-(piperazin-1-yl)phenyl]-2-(2-propyl)-2H-1,2,4-triazol-3-one,

2-(2-hydroxypropyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one,

4-[4-(piperazin-1-yl)phenyl]-2-[2-(4-trifluoromethyl)benzyl]-2H-1,2,4-triazol-3-one,

4-[4-(piperazin-1-yl)phenyl]-2-[2-(2,2,3,3-tetrafluoro)propyl]-2H-1,2,4-triazol-3-one,

4-[4-(piperazin-1-yl)phenyl]-2-[2-(3,3,3-trifluoroethyl)]-2H-1,2,4-triazol-3-one,

2-(2,4-difluorobenzyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one,

4-[4-(piperazin-1-yl)phenyl]-2-(4-trifluoromethoxybenzyl)-2H-1,2,4 -triazol-3-one,

2-(4-methoxybenzyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one,

2-(2,4-bis-trifluoromethylbenzyl)-4-[4-(piperazin-1-yl)phenyl]-2H-1,2,4-triazol-3-one,

4-[4-(piperazin-1-yl)phenyl]-2-[4-(2,2,3,3-tetrafluoropropoxy)benzyl]-2H-1,2,4-triazol-3-one, and

4-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-(4-trifluoromethylbenzyl)-2H-1,2,4-triazol-3-one.

23. A pharmaceutical composition suitable for treating a fungal infection, comprising a pharmaceutically effective amount of the compound of claim 1 in combination with a pharmaceutically acceptable carrier or diluent.

24. The pharmaceutical composition according to claim 23, wherein the pharmaceutical composition is an oral formulation and the compound is present in an amount of 1 to 25 % (w/w).

25. The pharmaceutical composition according to claim 23, wherein the pharmaceutical composition is an injectable formulation and the compound is present in an amount of 0.1 to 5 % (w/w).

26. The pharmaceutical composition according to claim 23, wherein the pharmaceutical composition is a topical or rectal formulation and the compound is present in an amount of 1 to 10 % (w/w).

27. A method of treating or preventing a fungal infection in a patient in need of such treatment or prevention, comprising administering to the patient a fungal infection treating- or preventing-amount of the compound of claim 1.

28. The method according to claim 27, wherein the compound is administered in a daily dose of 0.01 to 20 mg/kg patient.

29. The method according to claim 28, wherein the daily dose is divided into a plurality of individual doses.

30. The method according to claim 27, wherein the fungal infection is a topical infection.

31. The method according to claim 27, wherein the fungal infection is a systemic infection.

32. The method according to claim 27, wherein the fungal infection is a mucosal infection.

33. The method according to claim 27, wherein the fungal infection is a lung-invasive infection.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IB 98/00046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D249/08 C07D403/12 C07D417/12 A61K31/495 C07D249/12
C07D249/14 C07D257/06 C07D277/42

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 738 962 A (G. HOLMWOOD ET AL.) 19 April 1988 see the whole document ---	1-33
Y	EP 0 321 131 A (PFIZER LIMITED) 21 June 1989 see the whole document ---	1-33
P,X	L. NEUVILLE ET AL.: "Solution phase combinatorial synthesis of arylpiperazines" TETRAHEDRON LETTERS, vol. 38, no. 23, 9 June 1997, OXFORD GB, pages 4091-4094, XP002058738 see the whole document -----	21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 1998	07. 04. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/IB 98/00046

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 26-33
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/IB 98/00046

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4738962 A	19-04-88	DE 3508909 A	18-09-86
		BR 8601052 A	25-11-86
		DK 114486 A	14-09-86
		EP 0198191 A	22-10-86
		JP 61212568 A	20-09-86
EP 321131 A	21-06-89	CA 1306253 A	11-08-92
		DK 686088 A	21-07-89
		JP 1190672 A	31-07-89
		US 4885294 A	05-12-89